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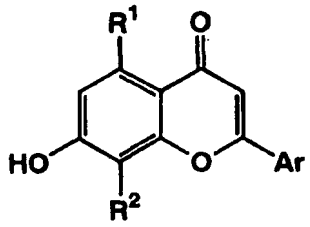

(I)

(57) Abstract

A medicament for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity or a neurodegenerative disease which comprises as an active ingredient a substance selected from the group consisting of a hydroxyflavone derivative represented by formula (I) and a salt thereof, and a solvate thereof and a hydrate thereof, wherein R^1 represents hydrogen atom or hydroxyl group; R^2 represents hydrogen atom or a C_1–C_{18} alkyl group which may have one or more C_6–C_{14} aryl groups; and Ar represents a C_6–C_{14} aryl group which may be substituted or an aromatic heterocyclic group which may be substituted.

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SPECIFICATION

HYDROXYFLAVONE DERIVATIVES AS TAU PROTEIN KINASE 1 INHIBITORS

Technical Field

The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases caused by tau protein kinase 1 hyperactivity, such as Alzheimer disease and the like. The present invention also relates to novel hydroxyflavone derivatives useful as an active ingredient of the aforementioned medicament.

Background Art

Alzheimer disease is progressive senile dementia, in which marked cerebral cortical atrophy is observed due to degeneration of nerve cells and decrease of nerve cell number. Pathologically, numerous senile plaques and neurofibrillary tangles are observed in brain. The number of patients has been increased with the increment of aged population, and the disease arises a serious social problem. Although various theories have been proposed, a cause of the disease has not yet been elucidated. Early resolution of the cause has been desired.

It has been known that the degree of appearance of two characteristic pathological changes of Alzheimer disease well correlates to the degree of intellectual dysfunction. Therefore, researches have been conducted from early 1980's to reveal the cause of the disease through molecular level investigations of components of the two pathological changes. Senile plaques accumulate extracellularly, and amyloid β protein has been

elucidated as their main component (abbreviated as "Aβ" hereinafter in the specification: Biochem. Biophys. Res. Commun.. 120, 855 (1984); EMBO J., 4, 2757 (1985); Proc. Natl. Acad. Sci. USA, 82. 4245 (1985)). In the other pathological change, i.e., the neurofibrillary tangles, a double-helical filamentous substance called paired helical filament (abbreviated as "PHF" hereinafter in the specification) accumulate intracellularly, and tau protein, which is a kind of microtubule-associated protein specific for brain. has been revealed as its main component (Proc. Natl. Acad. Sci. USA, 85, 4506 (1988); Neuron, 1, 827 (1988)).

Furthermore, on the basis of genetic investigations, presenilins 1 and 2 were found as causative genes of familial Alzheimer disease (Nature, 375, 754 (1995); Science, 269, 973 (1995); Nature. 376, 775 (1995)), and it has been revealed that presence of mutants of presenilins 1 and 2 promotes the secretion of Aβ (Neuron, 17, 1005 (1996); Proc. Natl. Acad. Sci. USA, 94, 2025 (1997)). From these results, it is considered that, in Alzheimer disease, Aβ abnormally accumulates and agglomerates due to a certain reason, which engages with the formation of PHF to cause death of nerve cells. It is also expected that extracellular outflow of glutamic acid and activation of glutamate receptor responding to the outflow may possibly be important factors in an early process of the nerve cell death caused by ischemic cerebrovascular accidents (Sai-shin Igaku [Latest Medicine], 49, 1506 (1994)).

It has been reported that kainic acid treatment that stimulates the AMPA receptor, one of glutamate receptor, increases mRNA of the amyloid precursor protein (abbreviated as "APP" hereinafter in the specification) as a precursor of Aβ (Society for Neuroscience Abstracts. 17, 1445 (1991)), and also promotes metabolism of APP (The Journal of Neuroscience, 10, 2400

(1990)). Therefore, it has been strongly suggested that the accumulation of Aβ is involved in cellular death due to ischemic cerebrovascular disorders. Other diseases in which abnormal accumulation and agglomeration of Aβ are observed include, for example, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, Lewy body disease (Shin-kei Shinpo [Nerve Advance], 34, 343 (1990); Tanpaku-shitu Kaku-san Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)) and the like. Furthermore, as diseases showing neurofibrillary tangles due to the PHF accumulation, examples include progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease and the like (Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 36, 2 (1991); Igaku no Ayumi [Progress of Medicine], 158, 511 (1991); Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)).

The tau protein is generally composed of a group of related proteins that forms several bands at molecular weights of 48-65 kDa in SDS-polyacrylamide gel electrophoresis, and it promotes the formation of microtubules. It has been verified that tau protein incorporated in the PHF in the brain suffering from Alzheimer disease is abnormally phosphorylated compared with usual tau protein (J. Biochem., 99, 1807 (1986); Proc. Natl. Acad. Sci. USA, 83, 4913 (1986)). An enzyme catalyzing the abnormal phosphorylation has been isolated. The protein was named as tau protein kinase 1 (abbreviated as "TPK1" hereinafter in the specification), and its physicochemical properties have been elucidated (Seikagaku [Biochemistry], 64, 308 (1992); J. Biol. Chem., 267, 10897 (1992)). Moreover, cDNA of rat TPK1 was cloned from a rat cerebral cortex cDNA library based on a partial amino acid sequence of TPK1, and its nucleotide sequence was determined

and an amino acid sequence was deduced (Japanese Patent Un-examined Publication [Kokai] No. 6-239893/1994). As a result, it has been revealed that the primary structure of the rat TPK1 corresponds to that of the enzyme known as rat GSK-3 β (glycogen synthase kinase 3β, FEBS Lett., 325, 167 (1993)).

It has been reported that Aβ, the main component of senile plaques, is neurotoxic (Science, 250, 279 (1990)). However, various theories have been proposed as for the reason why Aβ causes the cell death, and any authentic theory has not yet been established. Takashima et al. observed that the cell death was caused by Aβ treatment of fetal rat hippocampus primary culture system. and then found that the TPK1 activity was increased by Aβ treatment and the cell death by Aβ was inhibited by antisense of TPK1 (Proc. Natl. Acad. Sci. USA, 90, 7789 (1993); Japanese Patent Un-examined Publication [Kokai] No. 6-329551/1994).

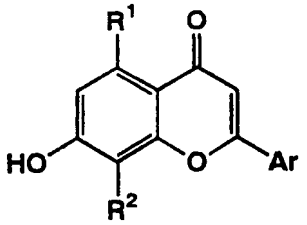
In view of the foregoing, compounds which inhibit the TPK1 activity may possibly suppress the neurotoxicity of Aβ and the formation of PHF and inhibit the nerve cell death in the Alzheimer disease, thereby cease or defer the progress of the disease. The compounds may also be possibly used as a medicament for therapeutic treatment of ischemic cerebrovascular disorder, Down syndrome, cerebral amyloid angiopathy, cerebral bleeding due to Lewy body disease and the like by suppressing the cytotoxicity of Aβ. Furthermore, the compounds may possibly be used as a medicament for therapeutic treatment of neurodegenerative diseases such as progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia.

Disclosure of the Invention

An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases such as Alzheimer disease and the like. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables radical prevention and/or treatment of the diseases such as Alzheimer disease by inhibiting the TPK1 activity to suppress the neurotoxicity of Aβ and the formation of the PHF and by inhibiting the drop of nerve cells. Another object of the present invention is to provide novel compounds useful as an active ingredient of the medicament haveing the aforementioned features.

In order to achieve the foregoing object, the inventors of the present invention conducted screenings of various compounds having inhibitory activity against the phosphorylation of TPK1. As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases. The present invention was achieved on the basis of these findings.

The present invention thus provides a medicament for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity or a neurodegenerative disease which comprises as an active ingredient a substance selected from the group consisting of a hydroxyflavone derivative represented by formula (I):



(I)

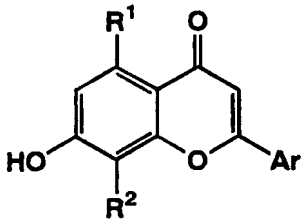
wherein R^1 represents hydrogen atom or hydroxyl group; R^2 represents hydrogen atom or a C_1-C_{18} alkyl group which may have a C_6-C_{14} aryl group; and Ar represents a C_6-C_{14} aryl group which may be substituted or an aromatic heterocyclic group which may be substituted and a salt thereof, and a solvate thereof and a hydrate thereof.

According to a preferred embodiment of the present invention, there is provided the aforementioned medicament wherein the diseases are selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia. Also as a preferred embodiment, the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives. The present invention further provides an inhibitor of tau protein kinase 1 selected from the group of the hydroxyflavone derivatives of formula (I) and the salts thereof, and the solvates thereof and the hydrates thereof.

According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of diseases caused by tau protein kinase 1 hyperactivity, which comprises the step of

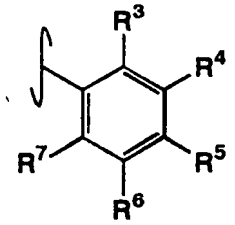
administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the hydroxyflavone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof; and a use of a substance selected from the group consisting of the hydroxyflavone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof for the manufacture of the aforementioned medicament.

According to still further aspect of the preset invention, there is provided a hydroxyflavone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:



(I)

wherein R^1 represents hydrogen atom or hydroxyl group; R^2 represents hydrogen atom or a C_1-C_{18} alkyl group which may have a C_6-C_{14} aryl group; and Ar represents a C_6-C_{14} aryl group which may be substituted or an aromatic heterocyclic group which may be substituted, and where R^2 is hydrogen atom, Ar represents a group represented by formula (II)



(II)

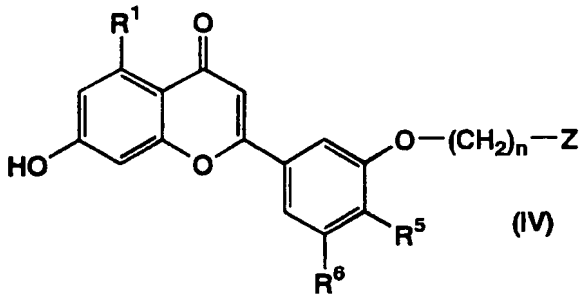
wherein R^3, R^4, R^5, R^6, and R^7, independently represent hydrogen atom, a C_1-C_{18} alkyl group which may be substituted, a C_1-C_{18} alkoxyl group which may be substituted, hydroxyl group, an acyloxy group which may be substituted, carboxyl group, an alkoxycarbonyl group which may be substituted, a carbamoyl group which may be substituted, an alkylcarbonyl group which may be substituted, an amino group which may be substituted, nitro group, or a cyano group,

provided that any one of R^3, R^4, R^5, R^6, and R^7 represents a group represented by formula (III): $-X-(CH_2)_m-R^8$ wherein R^8 represents an amino group which may be substituted or a nitrogen-containing saturated heterocyclic group which may be substituted, X represents single bond or oxygen atom, and m is an integer of from 1 to 8; and

provided that those wherein R^1 is hydrogen atom, R^2 is methyl group, and Ar is phenyl group, a 3,4-methylenedioxyphenyl group, or a 3-pyridyl group, those wherein R^1 is hydrogen atom, R^2 is propyl group, and Ar is phenyl group having a carboxyl group or an ester group in the 4-position, and those wherein R^1 is hydroxyl group, R^2 is methyl group, and Ar is phenyl group, 4-hydroxyphenyl group, 4-methoxyphenyl group, or 3,4-dimethoxyphenyl group are excluded.

According to preferred embodiments of the aforementioned invention, there are provided:

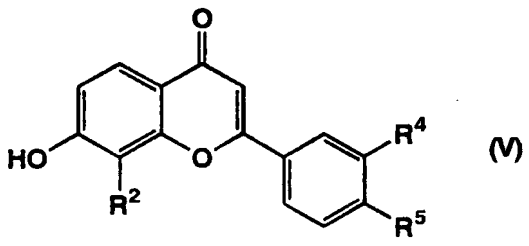
a hydroxyflavone derivative represented by formula (IV) or a salt thereof, or a solvate thereof or a hydrate thereof:



(IV)

wherein R^1 represents hydrogen atom or hydroxyl group; Z represents an amino group which may be substituted or a nitrogen-containing saturated heterocyclic group which may be substituted; n represents an integer of from 1 to 8; R^5 represents hydrogen atom, a C_1-C_{15} alkoxyl group; and R^6 represents hydrogen atom or hydroxyl group;

a hydroxyflavone derivative represented by formula (V) or a salt thereof, or a solvate thereof or a hydrate thereof:

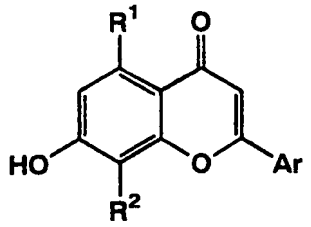


(V)

wherein R^2 represents hydrogen atom or a C_1-C_{18} alkyl group which may have one or more C_6-C_{14} aryl groups; R^4 represents a C_1-C_{18} alkyl group which may be substituted, a C_1-C_{18} alkoxyl group which may be substituted, hydroxyl group, an acyloxy group which may be substituted, carboxyl group, an alkoxycarbonyl group which may be substituted, a carbamoyl group which may be substituted, an alkylcarbonyl group which may be substituted, an amino group which may be substituted, nitro group, or a cyano group; and R^5 represents hydrogen atom, hydroxyl group, methoxy group, or nitro group;

and

a hydroxyflavone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:



(I)

wherein R^1 represents hydrogen atom or hydroxyl group; R^2 represents hydrogen atom or a C_1-C_{18} alkyl group which may have one or more C_6-C_{14} aryl groups; and Ar represents an aromatic heterocyclic group which may be substituted, provided that those wherein R^1 is hydrogen atom; R^2 is methyl group, and Ar is a pyridyl group are excluded.

Indian J. Chem. Sect. B, Org. Chem. Incl. Med. Chem., 35B, 1253 (1996) discloses compounds of the aforementioned formula (I) wherein R^1 is hydrogen atom, R^2 is allyl group, and Ar is phenyl group, 4-tolyl group, or 4-chlorophenyl group; Indian J. Chem. Sect. B. 30B. 93 (1991) discloses compounds of the aforementioned formula (I) wherein R^1 is hydrogen atom, R^2 is 1-phenyl-2-propenyl group, or 1-phenyl-1-propenyl group, and Ar is phenyl group; Indian J. Chem. Sect. B, 26B, 229 (1991), J. Indian Chem. Soc., 60, 411 (1983), and Indian J. Indian Chem. Soc., 49, 283 (1972) disclose compounds of the aforementioned formula (I) wherein R^1 is hydrogen atom, R^2 is methyl group, and Ar is phenyl group; Indian J. Chem. Sect. B, 19B, 866 (1980) discloses compounds of the aforementioned formula (I) wherein R^1 is hydrogen atom, R^2 is 1,2-dimethyl-2-propenyl group, and Ar is phenyl group; and Ann. Pharm. France, 18, 528 (1960), discloses compounds of the

aforementioned formula (I) wherein R^1 is hydrogen atom, R^2 is methyl group, and Ar is 3,4-methylenedioxyphenyl group.

Phytochemistry, 19, 2179 (1980) discloses compounds of the aforementioned formula (I) wherein R^1 is hydrogen atom, R^2 is 3-methyl-2-butenyl group, and Ar is 4-hydroxyphenyl group; Indian J. Chem. Sect. B, 18B, 525 (1979) discloses compounds of the aforementioned formula (I) wherein R^1 is hydrogen atom, R^2 is allyl group, and Ar is a phenyl group having methoxy group at 2-, 3- or 4-position; Indian J. Chem. Sect. B, 15B, 933 (1977) and Tetrahedron Lett., 1977, 473 (1977) disclose compounds of the aforementioned formula (I) wherein R^1 is hydrogen atom, R^2 is allyl group, and Ar is phenyl group; and Bull. Soc. Chim. FR1960, 95(1960) discloses compounds of the aforementioned formula (I) wherein R^1 is hydrogen atom, R^2 is methyl group, and Ar is 3-pyridyl group.

J. Indian Chem. Soc., 65, 149 (1988) and Indian J. Chem. Sect. B, 20B, 624 (1981) disclose compounds of the aforementioned formula (I) wherein R^1 is hydroxyl group, R^2 is methyl group, and Ar is 3,4-methylenedioxyphenyl group; Tetrahedron, 31, 265 (1975) discloses compounds of the aforementioned formula (I) wherein R^1 is hydroxyl group, R^2 is methyl group, and Ar is phenyl group; Indian J. Chem., 4, 481 (1966) discloses compounds of the aforementioned formula (I) wherein R^1 is hydroxyl group, R^2 is methyl group, and Ar is 4-methoxyphenyl group; and Phytochemistry, 22, 2107 (1983) discloses compounds of the aforementioned formula (I) wherein R^1 is hydroxyl group, R^2 is methyl group, and Ar is 4-hydroxyphenyl group.

Furthermore, U.S. Patent No. 4,042.708 and German Patent No. 2,454,670 disclose compounds of the aforementioned formula (I) wherein R^1 is hydroxyl group, R^2 is propyl group, and Ar is a phenyl group having

4-carboxyl group or 4-ethoxycarbonyl group as synthetic intermediates for preparation of compounds having anti-SRS activity, and Japanese Patent Un-examined Publication [Kokai] No. 8-225563/1996) discloses that compounds of the aforementioned formula (I) wherein R^1 is hydroxyl group, R^2 is propyl group, and Ar is 3-hydroxy-4-methylphenyl group are useful for treatment of chronic venous insufficiency. However, it has not hitherto been known at all that these compounds have inhibitory activity against TPK1.

Best Mode for Carrying Out the Invention

The "alkyl group" or an alkyl portion of a functional group containing the alkyl portion (alkoxyl group, for example) used herein may be either linear, cyclic or branched. The alkyl group represented by R^2 may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, cyclobutyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, cyclopentyl group, n-hexyl group, isohexyl group, cyclohexyl group, or a linear or branched heptyl group, octyl group, nonyl group, decyl group, undecyl group, dodecyl group, tridecyl group, tetradecyl group, pentadecyl group, octadecyl group or the like.

Examples of the C_1-C_{18} alkyl group having a C_6-C_{14} aryl group represented by R^2 include, for example, the aforementioned C_1-C_{18} alkyl groups which are substituted with phenyl group, naphthyl group, anthryl group or the like. More specifically, examples include benzyl group, 1-naphtylmethyl group, 2-naphtylmethyl group, 1-phenetyl group, 2-phenetyl group, 3-phenylpropyl group, 4-phenylbutyl group and the like. Examples of the C_6-C_{14} aryl group represented by Ar include, for example, phenyl

group, 1-naphthyl group, 2-naphthyl group, anthryl group and the like.

In the specification, when a functional group is defined as "which may be substituted" or "optionally substituted", the number of substituents as well as their types and substituting positions are not particularly limited, and when two or more substituents are present, they may be the same or different. When the aryl group represented by Ar has one or more substituents, the aryl group may have one or more substituents selected form the group consisting of a C_1-C_{18} alkyl group such as those explained above as for R^2; a C_1-C_8 alkoxyl group such as methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, isobutoxy group, tert-butoxy group, n-pentyloxy group, isopentyloxy group, cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group, cycloheptyloxy group, and cyclooctyloxy group; a C_1-C_8 alkylthio group such as methylthio group, ethylthio group, propylthio group, isopropylthio group, butylthio group, isobutylthio group, tert-butylthio group, pentylthio group; methylenedioxy group; a C_6-C_{10} aryl group such as phenyl group, 1-naphthyl group, and 2-naphthyl group; fluorenyl group; a C_6-C_{14} aryloxy group such as phenoxy group, and naphthoxy group; a C_6-C_{14} arylthio group such as phenylthio group, and naphthylthio group; a C_1-C_5 alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a C_6-C_{14} arylsulfonyl group such as phenylsulfonyl group, and naphthylsulfonyl group; a halogen atom (the term "halogen atom" or "halogen" used herein encompasses any one of fluorine atom, chlorine atom, bromine atom, and iodine atom); a C_1-C_{18} halogenated alkyl group such as trifluoromethyl group; hydroxyl group; nitro group; oxo group; formyl group; cyano group; carboxyl group; a C_2-C_6 alkyloxycarbonyl group such as methoxycarbonyl group,

ethoxycarbonyl group, propoxycarbonyl group, isopropoxycarbonyl group, butoxycarbonyl group, isobutoxycarbonyl group, tert-butoxycarbonyl group, and pentyloxycarbonyl group; a C_2-C_6 alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; a C_2-C_6 alkylcarbonyloxy group such as acetoxy group, propionyloxy group, butyryloxy group, and valeryloxy group; a C_6-C_{14} arylcarbonyloxy group such as benzoyloxy group, and naphthoyloxy group; amino group; a C_1-C_5 monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C_2-C_{10} dialkylamino group (two alkyl groups may be the same or different from each other) such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; a C_2-C_6 alkylcarbonylamino group such as acetylamino group, propionylamino group, isopropionylamino group, butyrylamino group, and valerylamino group; carbamoyl group; a C_2-C_6 alkylcarbamoyl group such as methylcarbamoyl group, ethylcarbamoyl group, propylcarbamoyl group, butylcarbamoyl group, tert-butylcarbamoyl group, and pentylcarbamoyl group; a C_3-C_9 dialkylcarbamoyl group such as dimethylcarbamoyl group, diethylcarbamoyl group, dipropylcarbamoyl group, diisopropylcarbamoyl group, and dibutylcarbamoyl group; and a residue of heterocyclic ring having 1-4 heteroatoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10, for example, furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, isobenzofuran ring, chromene ring, chroman ring, isochroman ring, thiophene ring, benzothiophene ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring,

imidazolidine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indolizine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, purine ring, quinolizine ring, quinoline ring, phthalazine ring, naphtylidine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, dioxane ring, dithian ring, morpholine ring, thiomorpholine ring, phthalimide ring and the like (the group of these substituents is referred to as "substituent group A"). As for the substituent group A, the aryl group and the heterocyclic group may further have one or more substituents selected from the substituent group A.

Examples of the aromatic heterocyclic group represented by Ar include, for example, residues of aromatic heterocyclic rings each having 1-4 heteroatoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10. These aromatic heterocyclic groups may be bound at any position on the rings. More specifically, examples include residues of furan ring, benzofuran ring, isobenzofuran ring, thiophene ring, benzothiophene ring, pyrrole ring, imidazole ring, pyrazole ring, triazole ring, tetrazole ring, pyridine ring, pyrazine ring, pyrimidine ring, pyridazine ring, indole ring, isoindole ring, indazole ring, benzimidazole ring, purine ring, quinoline ring, isoquinoline ring, phthalazine ring, oxazole ring, isoxazole ring, thiazole ring, benzothiazole ring, isothiazole ring and the like. The aromatic heterocyclic group may have one or more substituents selected from the substituent group A.

Example of the C_1-C_{18} alkyl group represented by R^3 through R^7

include those explained above as for R^2, and the alkyl group may have one or more substituents selected from the substituent group A. Example of the alkoxyl group represented by R^3 through R^7 include, for example, C_1-C_{18} alkoxyl group such as methoxy group, ethoxy group, n-propoxy group, isopropoxy group, cyclopropyloxy group, n-butoxy group, isobutoxy group, tert-butoxy group, cyclobutoxy group, n-pentyloxy group, isopentyloxy group, cyclopentyloxy group, n-hexyloxy group, isohexyloxy group, cyclohexyloxy group, as well as linear, branched, or cyclic heptyloxy group, octyloxy group, nonyloxy group, decyloxy group, undecyloxy group, dodecyloxy group, tridecyloxy group, tetradecyloxy group, pentadecyloxy group, hexadecyloxy group, heptadecyloxy group, octadecyloxy group and the like. The alkoxyl group may have one or more substituents selected from the substituent group A.

Example of the acyloxy group represented by R^3 to R^7 include, for example, a C_2-C_6 alkylcarbonyloxy group such as acetoxy group, propionyloxy group, butyryloxy group, and valeryloxy group; and a C_6-C_{14} arylcarbonyloxy group such as benzoyloxy group and naphthoyloxy group. The alkyl portion of the alkylcarbonyloxy group and the aryl portion of the arylcarbonyloxy group may have one or more substituents selected from the substituent group A. Example of the alkoxycarbonyl group represented by R^3 through R^7 include, for example, a C_2-C_6 alkoxycarbonyl group such as methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group, isopropoxycarbonyl group, n-butoxycarbonyl group, isobutoxycarbonyl group, tert-butoxycarbonyl group, and n-pentyloxycarbonyl group. The alkyl portion of the alkoxycarbonyl group may have one or more substituents selected from the substituent group A.

When the carbamoyl group represented by R^3 through R^7 has one or

more substituents, examples of the carbamoyl group include, for example, a C_2-C_6 monoalkylcarbamoyl group such as methylcarbamoyl group, ethylcarbamoyl group, propylcarbamoyl group, butylcarbamoyl group, tert-butylcarbamoyl group, and pentylcarbamoyl group; a C_3-C_9 dialkylcarbamoyl group (two alkyl groups may be the same or different from each other) such as dimethylcarbamoyl group, diethylcarbamoyl group, dipropylcarbamoyl group, diisopropylcarbamoyl group, and dibutylcarbamoyl group and the like. The alkyl portions of the aforementioned alkylcarbamoyl group and the dialkylcarbamoyl group may have one or more substituents selected from the substituent group A.

Where the amino group represented by R^3 through R^7 has one or more substituents, examples include a C_1-C_6 monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C_2-C_{10} dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; a C_2-C_6 alkylcarbonylamino group such as acetylamino group, propionylamino group, isopropionylamino group, butyrylamino group, and valerylamino group and the like. The alkyl portions of the aforementioned monoalkylamino group and the dialkylamino group may have one or more substituents selected from the substituent group A. When the amino group represented by R^8 has one or more substituents, the group may be a substituted amino group selected from those explained above as for R^3 through R^7.

The number of nitrogen atoms contained in the nitrogen-containing saturated heterocyclic group represented by R^8 is not particularly limited, and the group may contain one or more heteroatoms other than nitrogen (e.g.,

oxygen atom, sulfur atom etc.). The nitrogen-containing saturated heterocyclic group may be substituted at any position on the ring. More specifically, examples include residues of pyrrolidine ring, piperidine ring, piperazine ring, homopiperidine ring, homopiperazine ring, morpholine ring, thiomorpholine ring and the like. The nitrogen-containing saturated heterocyclic group may be substituted with one or more substituents selected from the substituent group A.

When the amino group represented by Z has one or more substituents, the group may be a substituted amino group selected from those explained above as for R^3 through R^7. Examples of the nitrogen-containing saturated heterocyclic group represented by Z include pyrrolidine ring, pyrazolidine ring, imidazolidine ring, thiazolidine ring, piperidine ring, piperazine ring, morpholine ring, thiomorpholine ring, quinuclidine ring and the like.

In addition to the compounds represented by the aforementioned formula (I), physiologically acceptable salts thereof may be used as the active ingredient of the medicament of the present invention. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine, δ-hydroxylysine, and arginine. When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid,

maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or salts with acidic amino acids such as aspartic acid, and glutamic acid.

Solvates and hydrates of the hydroxyflavone derivatives represented by the aforementioned formula (I) and salts thereof may also be used as the active ingredient of the medicament of the present invention. Furthermore, the hydroxyflavone derivatives represented by the aforementioned formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) or (S) configuration, and the hydroxyflavone derivatives may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers of pure form, any mixtures of stereoisomers, racemates and the like may be used as the active ingredient of the medicament of the present invention. Furthermore, 4-keto and 4-hydroxy compounds of the hydroxyflavone derivatives represented by the aforementioned formula (I) may exist as tautomers. The existence of the tautomers is readily apparent to those skilled in the art, and any of the tautomers also fall within the scope of the present invention.

Examples of preferred compounds of the present invention are shown in the tables below. However, the scope of the present invention is not limited by the following compounds.

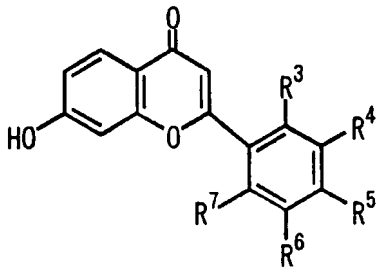


Table-1

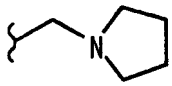
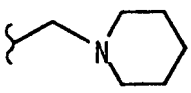
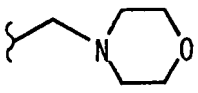
Compound No.	R^3	R^4	R^5	R^6	R^7
1		H	H	H	H
2		H	H	H	H
3		H	H	H	H
4		H	H	H	H
5		H	H	H	H
6		H	H	H	H
7		H	H	H	H

Table-1(continued)

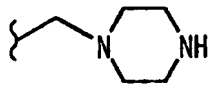
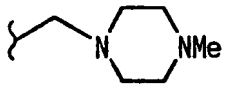
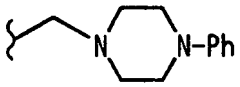
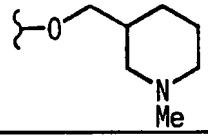
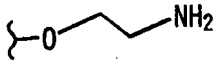
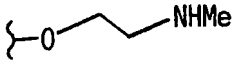
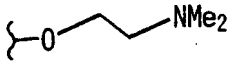
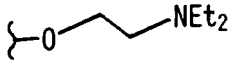
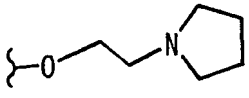
Compound No.	R^3	R^4	R^5	R^6	R^7
8		H	H	H	H
9		H	H	H	H
10		H	H	H	H
11		H	H	H	H
12		H	H	H	H
13		H	H	H	H
14		H	H	H	H
15		H	H	H	H
16		H	H	H	H

Table-1(continued)

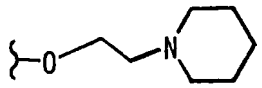
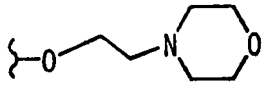
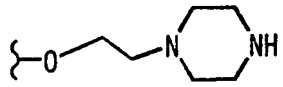
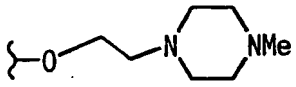
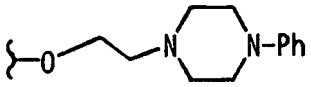
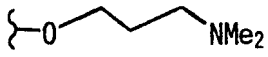
Compound No.	R^3	R^4	R^5	R^6	R^7
17		H	H	H	H
18		H	H	H	H
19		H	H	H	H
20		H	H	H	H
21		H	H	H	H
22		H	H	H	H
23		H	H	H	H
24		H	H	H	H
25		H	H	H	H

Table-1(continued)

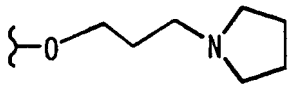
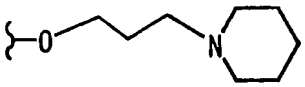
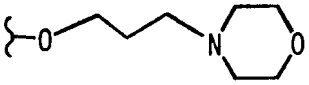
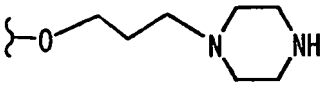
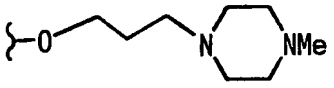
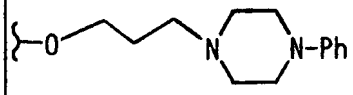
Compound No.	R^3	R^4	R^5	R^6	R^7
26		H	H	H	H
27		H	H	H	H
28		H	H	H	H
29		H	H	H	H
30		H	H	H	H
31		H	H	H	H

Table-1(continued)

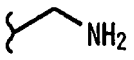
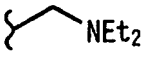
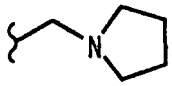
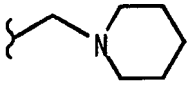
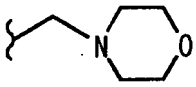
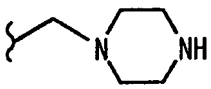
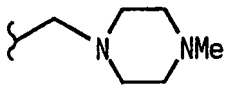
Compound No.	R^3	R^4	R^5	R^6	R^7
32	H		H	H	H
33	H		H	H	H
34	H		H	H	H
35	H		H	H	H
36	H		H	H	H
37	H		H	H	H
38	H		H	H	H
39	H		H	H	H
40	H		H	H	H

Table-1(continued)

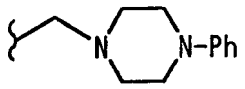
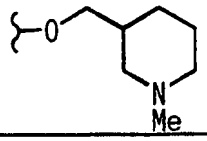
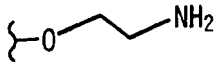
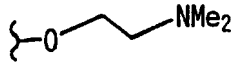
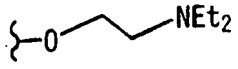
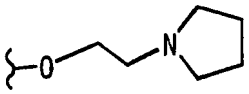
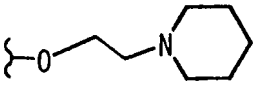
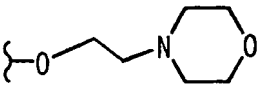
Compound No.	R^3	R^4	R^5	R^6	R^7
41	H		H	H	H
42	H		H	H	H
43	H		H	H	H
44	H		H	H	H
45	H		H	H	H
46	H		H	H	H
47	H		H	H	H
48	H		H	H	H
49	H		H	H	H

Table-1(continued)

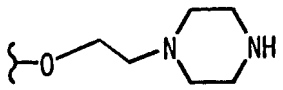
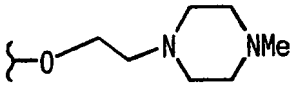
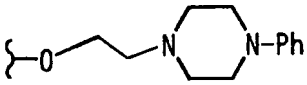
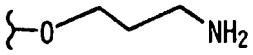
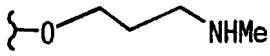
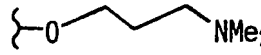
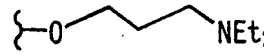
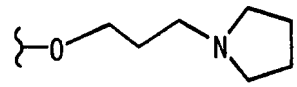
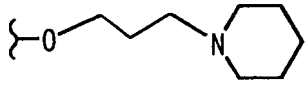
Compound No.	R^3	R^4	R^5	R^6	R^7
50	H		H	H	H
51	H		H	H	H
52	H		H	H	H
53	H		H	H	H
54	H		H	H	H
55	H		H	H	H
56	H		H	H	H
57	H		H	H	H
58	H		H	H	H

Table-1(continued)

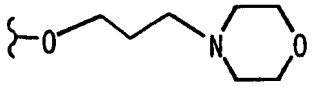
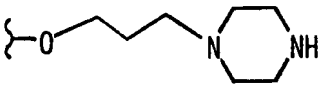
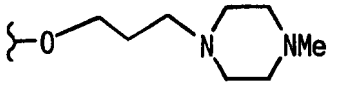
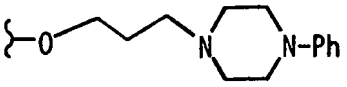
Compound No.	R^3	R^4	R^5	R^6	R^7
59	H		H	H	H
60	H		H	H	H
61	H		H	H	H
62	H		H	H	H

Table-1(continued)

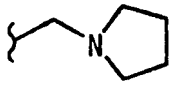
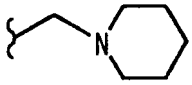
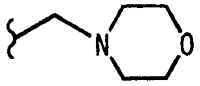
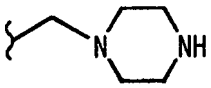
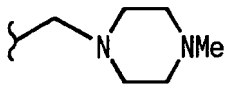
Compound No.	R^3	R^4	R^5	R^6	R^7
63	H	H		H	H
64	H	H		H	H
65	H	H		H	H
66	H	H		H	H
67	H	H		H	H
68	H	H		H	H
69	H	H		H	H
70	H	H		H	H
71	H	H		H	H

Table-1(continued)

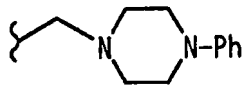
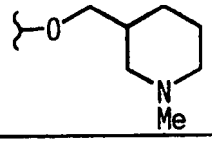
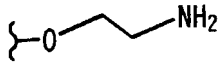
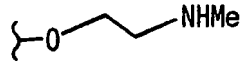
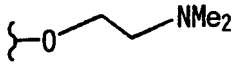
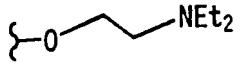
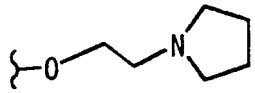
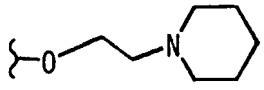
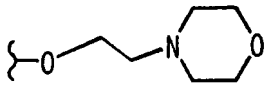
Compound No.	R^3	R^4	R^5	R^6	R^7
72	H	H		H	H
73	H	H		H	H
74	H	H		H	H
75	H	H		H	H
76	H	H		H	H
77	H	H		H	H
78	H	H		H	H
79	H	H		H	H
80	H	H		H	H

Table-1(continued)

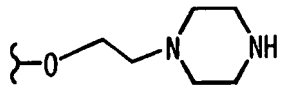
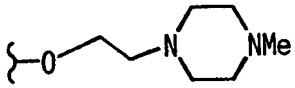
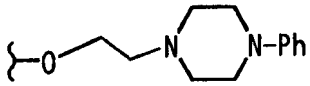
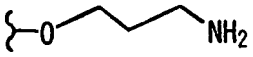
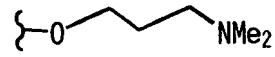
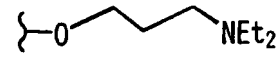
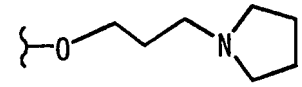
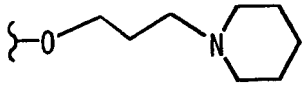
Compound No.	R^3	R^4	R^5	R^6	R^7
81	H	H		H	H
82	H	H		H	H
83	H	H		H	H
84	H	H		H	H
85	H	H		H	H
86	H	H		H	H
87	H	H		H	H
88	H	H		H	H
89	H	H		H	H

Table-1(continued)

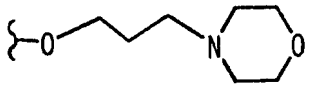
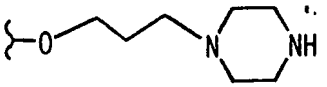
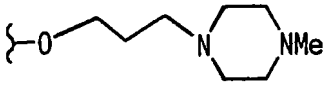
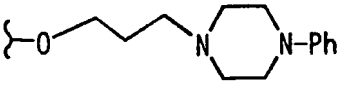
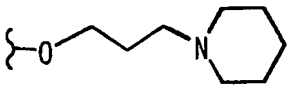
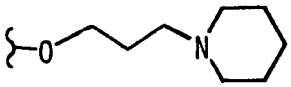
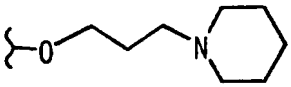
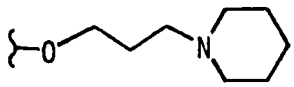
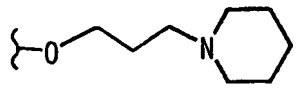
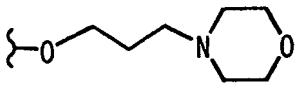
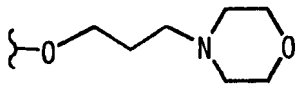
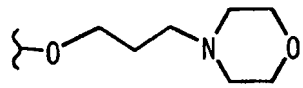
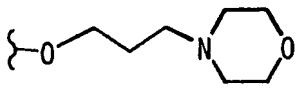
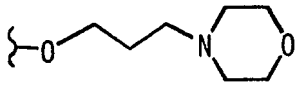
Compound No.	R^3	R^4	R^5	R^6	R^7
90	H	H		H	H
91	H	H		H	H
92	H	H		H	H
93	H	H		H	H

Table-1(continued)

Compound No.	R^3	R^4	R^5	R^6	R^7
94	H		NO_2	H	H
95	H		NH_2	H	H
96	H		OMe	H	H
97	H		H	OMe	H
98	H		H	OH	H
99	H		NO_2	H	H
100	H		NH_2	H	H
101	H		OMe	H	H
102	H		H	OMe	H
103	H		H	OH	H

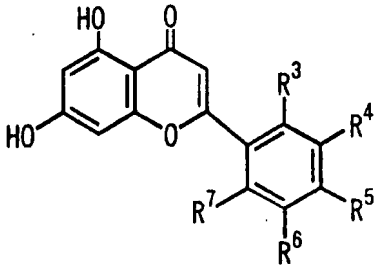


Table-2

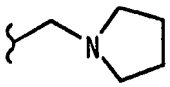
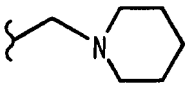
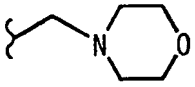
Compound No.	R^3	R^4	R^5	R^6	R^7
104		H	H	H	H
105		H	H	H	H
106		H	H	H	H
107		H	H	H	H
108		H	H	H	H
109		H	H	H	H
110		H	H	H	H

Table-2(continued)

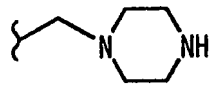
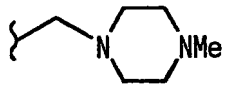
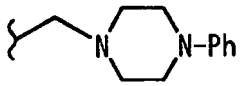
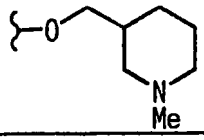
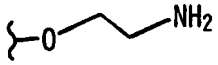
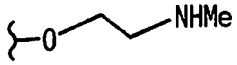
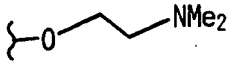
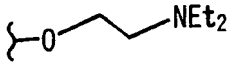
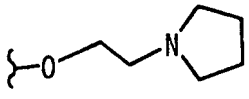
Compound No.	R^3	R^4	R^5	R^6	R^7
111		H	H	H	H
112		H	H	H	H
113		H	H	H	H
114		H	H	H	H
115		H	H	H	H
116		H	H	H	H
117		H	H	H	H
118		H	H	H	H
119		H	H	H	H

Table-2(continued)

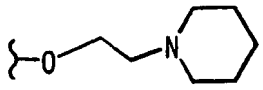
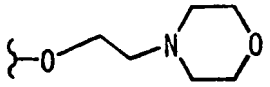
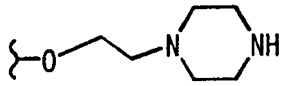
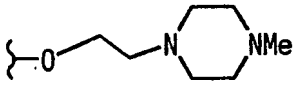
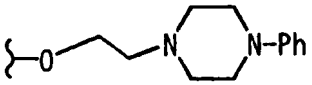
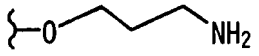
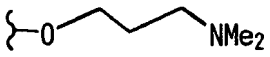
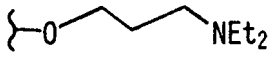
Compound No.	R^3	R^4	R^5	R^6	R^7
120		H	H	H	H
121		H	H	H	H
122		H	H	H	H
123		H	H	H	H
124		H	H	H	H
125		H	H	H	H
126		H	H	H	H
127		H	H	H	H
128		H	H	H	H

Table-2(continued)

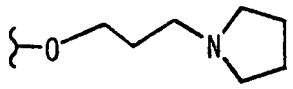
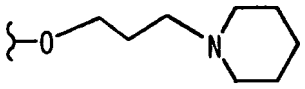
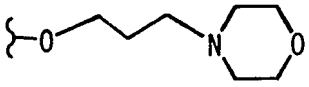
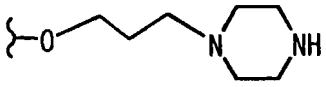
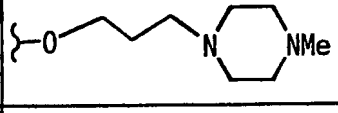
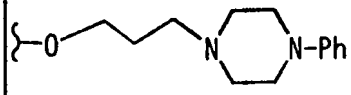
Compound No.	R^3	R^4	R^5	R^6	R^7
129		H	H	H	H
130		H	H	H	H
131		H	H	H	H
132		H	H	H	H
133		H	H	H	H
134		H	H	H	H

Table-2(continued)

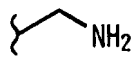
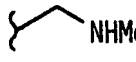
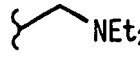
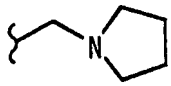
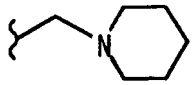
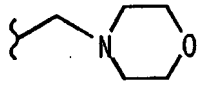
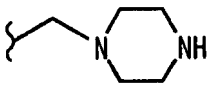
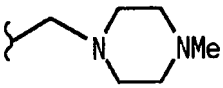
Compound No.	R^3	R^4	R^5	R^6	R^7
135	H		H	H	H
136	H		H	H	H
137	H		H	H	H
138	H		H	H	H
139	H		H	H	H
140	H		H	H	H
141	H		H	H	H
142	H		H	H	H
143	H		H	H	H

Table-2(continued)

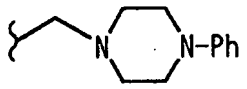
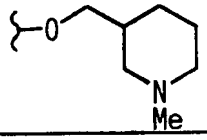
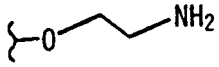
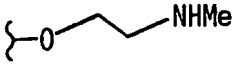
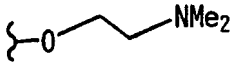
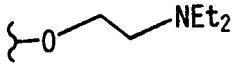
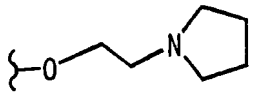
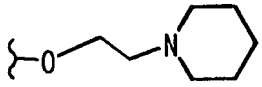
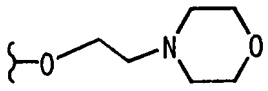
Compound No.	R^3	R^4	R^5	R^6	R^7
144	H		H	H	H
145	H		H	H	H
146	H		H	H	H
147	H		H	H	H
148	H		H	H	H
149	H		H	H	H
150	H		H	H	H
151	H		H	H	H
152	H		H	H	H

Table-2(continued)

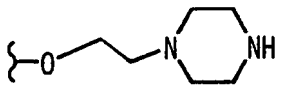
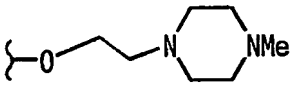
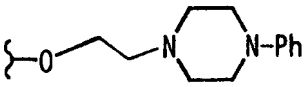
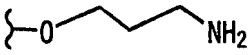
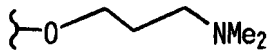
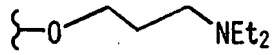
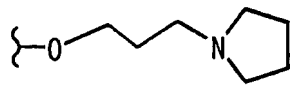
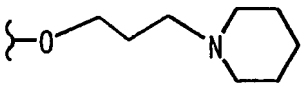
Compound No.	R^3	R^4	R^5	R^6	R^7
153	H		H	H	H
154	H		H	H	H
155	H		H	H	H
156	H		H	H	H
157	H		H	H	H
158	H		H	H	H
159	H		H	H	H
160	H		H	H	H
161	H		H	H	H

Table-2(continued)

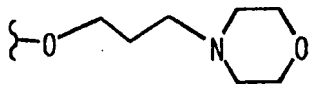
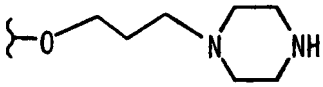
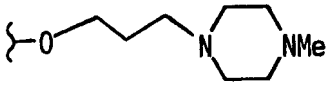
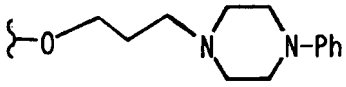
Compound No.	R^3	R^4	R^5	R^6	R^7
162	H		H	H	H
163	H		H	H	H
164	H		H	H	H
165	H		H	H	H

Table-2(continued)

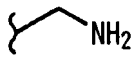
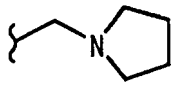
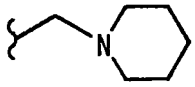
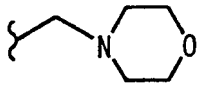
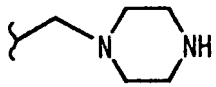
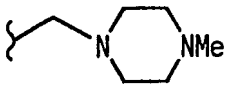
Compound No.	R^3	R^4	R^5	R^6	R^7
166	H	H		H	H
167	H	H		H	H
168	H	H		H	H
169	H	H		H	H
170	H	H		H	H
171	H	H		H	H
172	H	H		H	H
173	H	H		H	H
174	H	H		H	H

Table-2(continued)

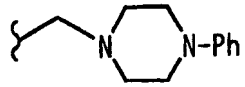
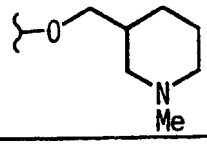
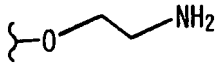
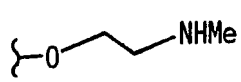
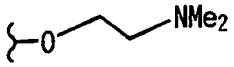
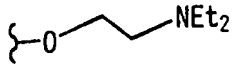
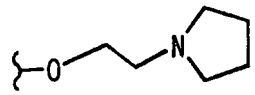
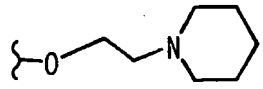
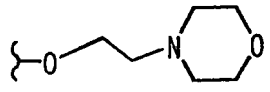
Compound No.	R^3	R^4	R^5	R^6	R^7
175	H	H		H	H
176	H	H		H	H
177	H	H		H	H
178	H	H		H	H
179	H	H		H	H
180	H	H		H	H
181	H	H		H	H
182	H	H		H	H
183	H	H		H	H

Table-2(continued)

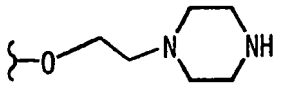
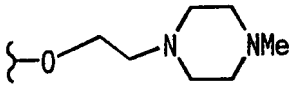
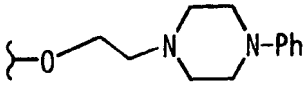
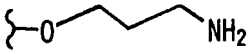
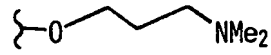
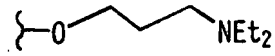
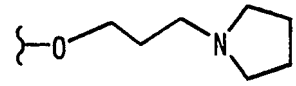
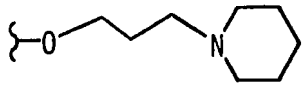
Compound No.	R^3	R^4	R^5	R^6	R^7
184	H	H		H	H
185	H	H		H	H
186	H	H		H	H
187	H	H		H	H
188	H	H		H	H
189	H	H		H	H
190	H	H		H	H
191	H	H		H	H
192	H	H		H	H

Table-2(continued)

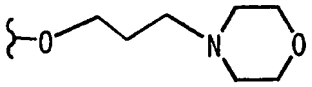
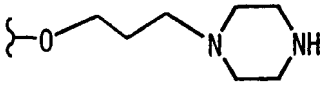
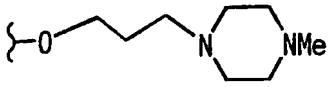
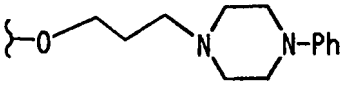
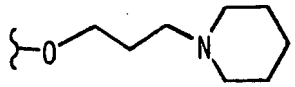
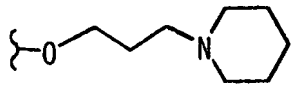
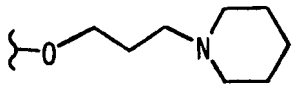
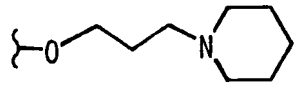
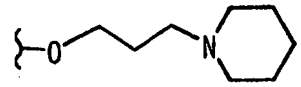
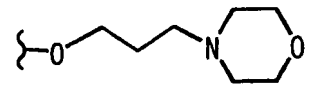
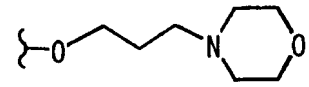
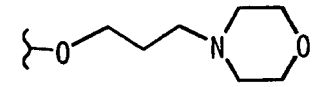
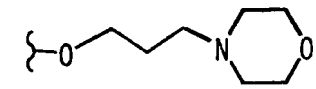
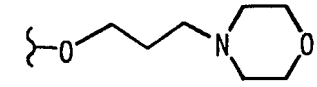
Compound No.	R^3	R^4	R^5	R^6	R^7
193	H	H		H	H
194	H	H		H	H
195	H	H		H	H
196	H	H		H	H

Table-2(continued)

Compound No.	R^3	R^4	R^5	R^6	R^7
197	H		NO_2	H	H
198	H		NH_2	H	H
199	H		OMe	H	H
200	H		H	OMe	H
201	H		H	OH	H
202	H		NO_2	H	H
203	H		NH_2	H	H
204	H		OMe	H	H
205	H		H	OMe	H
206	H		H	OH	H

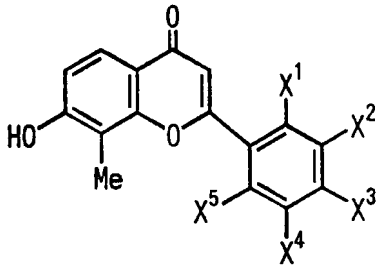


Table-3

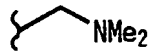
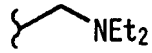
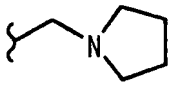
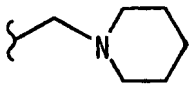
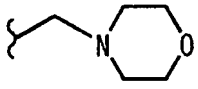
Compound No.	X^1	X^2	X^3	X^4	X^5
207		H	H	H	H
208		H	H	H	H
209		H	H	H	H
210		H	H	H	H
211		H	H	H	H
212		H	H	H	H
213		H	H	H	H

Table-3(continued)

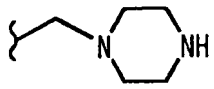
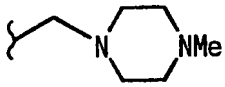
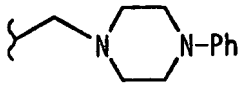
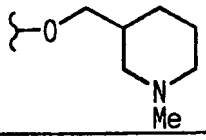
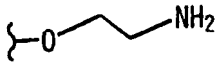
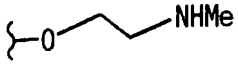
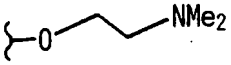
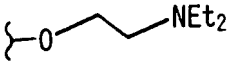
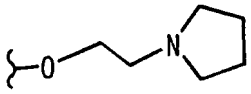
Compound No.	X^1	X^2	X^3	X^4	X^5
214		H	H	H	H
215		H	H	H	H
216		H	H	H	H
217		H	H	H	H
218		H	H	H	H
219		H	H	H	H
220		H	H	H	H
221		H	H	H	H
222		H	H	H	H

Table-3(continued)

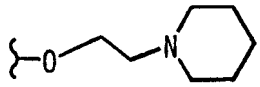
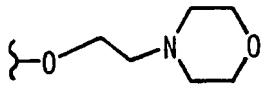
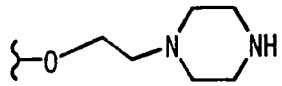
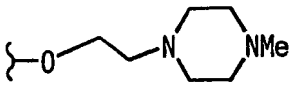
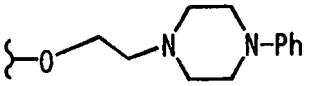
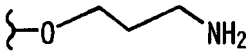
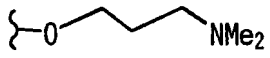
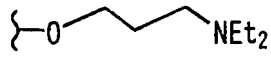
Compound No.	X^1	X^2	X^3	X^4	X^5
223		H	H	H	H
224		H	H	H	H
225		H	H	H	H
226		H	H	H	H
227		H	H	H	H
228		H	H	H	H
229		H	H	H	H
230		H	H	H	H
231		H	H	H	H

Table-3(continued)

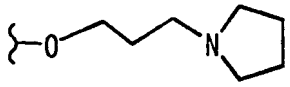
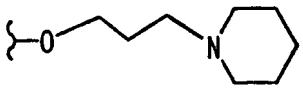
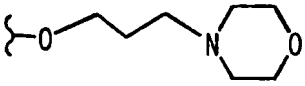
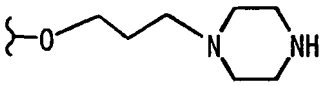
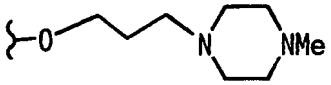
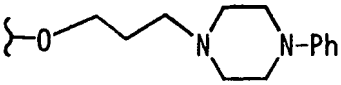
Compound No	X^1	X^2	X^3	X^4	X^5
232		H	H	H	H
233		H	H	H	H
234		H	H	H	H
235		H	H	H	H
236		H	H	H	H
237		H	H	H	H

Table-3(continued)

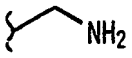
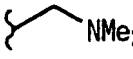
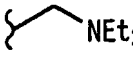
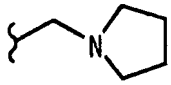
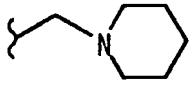
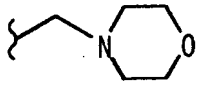
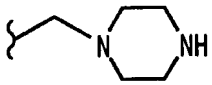
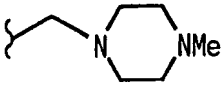
Compound No.	X^1	X^2	X^3	X^4	X^5
238	H		H	H	H
239	H		H	H	H
240	H		H	H	H
241	H		H	H	H
242	H		H	H	H
243	H		H	H	H
244	H		H	H	H
245	H		H	H	H
246	H		H	H	H

Table-3(continued)

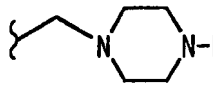
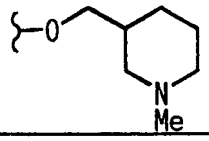
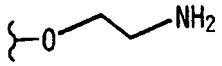
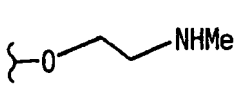
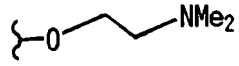
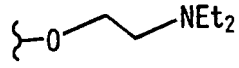
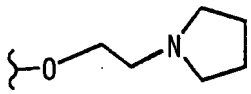
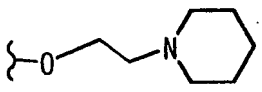
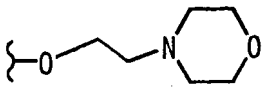
Compound No.	X^1	X^2	X^3	X^4	X^5
247	H		H	H	H
248	H		H	H	H
249	H		H	H	H
250	H		H	H	H
251	H		H	H	H
252	H		H	H	H
253	H		H	H	H
254	H		H	H	H
255	H		H	H	H

Table-3(continued)

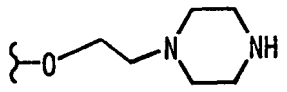
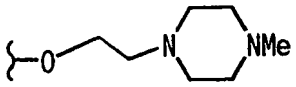
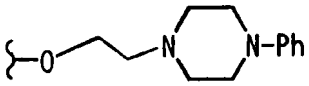
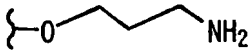
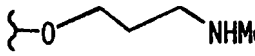
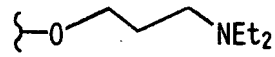
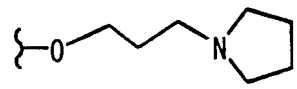
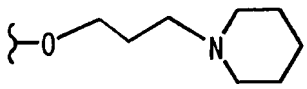
Compound No.	X^1	X^2	X^3	X^4	X^5
256	H		H	H	H
257	H		H	H	H
258	H		H	H	H
259	H		H	H	H
260	H		H	H	H
261	H		H	H	H
262	H		H	H	H
263	H		H	H	H
264	H		H	H	H

Table-3(continued)

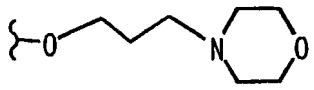
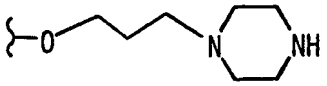
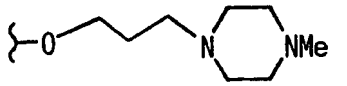
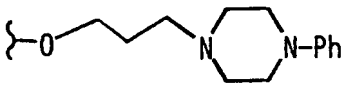
Compound No.	X^1	X^2	X^3	X^4	X^5
265	H		H	H	H
266	H		H	H	H
267	H		H	H	H
268	H		H	H	H

Table-3(continued)

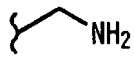
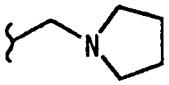
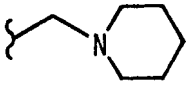
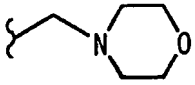
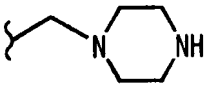
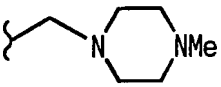
Compound No.	X^1	X^2	X^3	X^4	X^5
269	H	H		H	H
270	H	H		H	H
271	H	H		H	H
272	H	H		H	H
273	H	H		H	H
274	H	H		H	H
275	H	H		H	H
276	H	H		H	H
277	H	H		H	H

Table-3(continued)

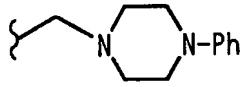
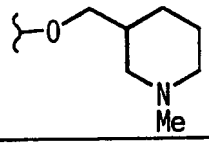
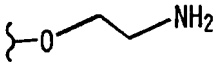
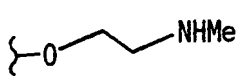
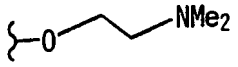
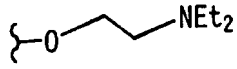
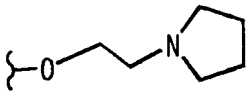
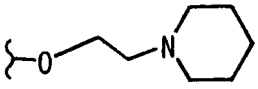
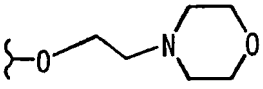
Compound No.	X^1	X^2	X^3	X^4	X^5
278	H	H		H	H
279	H	H		H	H
280	H	H		H	H
281	H	H		H	H
282	H	H		H	H
283	H	H		H	H
284	H	H		H	H
285	H	H		H	H
286	H	H		H	H

Table-3(continued)

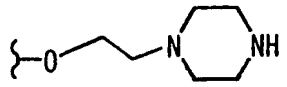
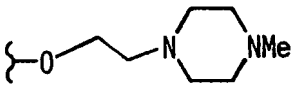
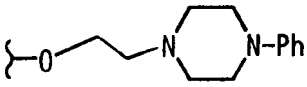
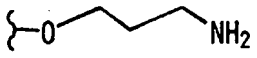
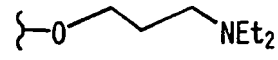
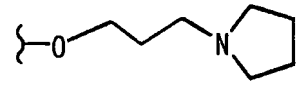
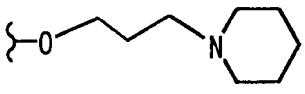
Compound No.	X^1	X^2	X^3	X^4	X^7
287	H	H		H	H
288	H	H		H	H
289	H	H		H	H
290	H	H		H	H
291	H	H		H	H
292	H	H		H	H
293	H	H		H	H
294	H	H		H	H
295	H	H		H	H

Table-3(continued)

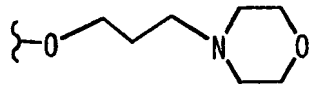
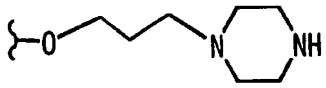
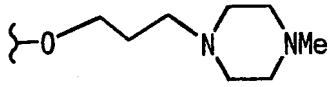
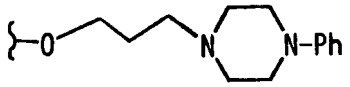
Compound No.	X^1	X^2	X^3	X^4	X^5
296	H	H		H	H
297	H	H		H	H
298	H	H		H	H
299	H	H		H	H

Table-3(continued)

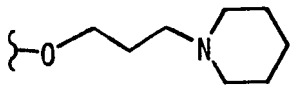
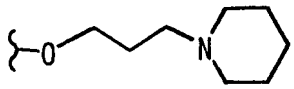
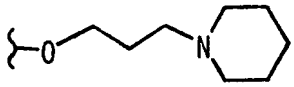
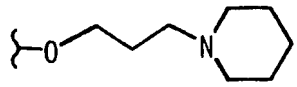
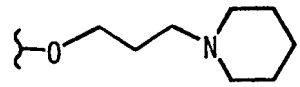
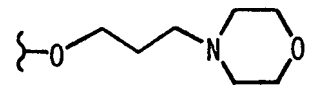
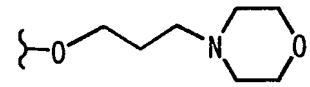
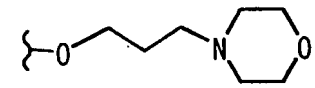
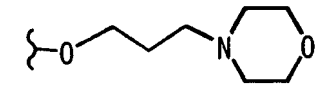
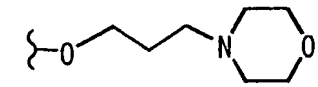
Compound No.	X^1	X^2	X^3	X^4	X^5
300	H		NO_2	H	H
301	H		NH_2	H	H
302	H		OMe	H	H
303	H		H	OMe	H
304	H		H	OH	H
305	H		NO_2	H	H
306	H		NH_2	H	H
307	H		OMe	H	H
308	H		H	OMe	H
309	H		H	OH	H

Table-3(continued)

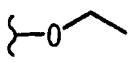
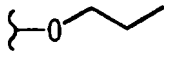
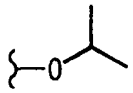
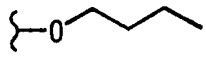
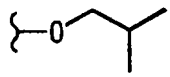
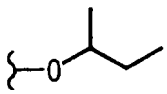
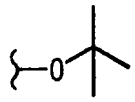
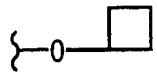
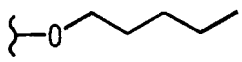
Compound No.	X^1	X^2	X^3	X^4	X^5
310	H		OH	H	H
311	H		OH	H	H
312	H		OH	H	H
313	H		OH	H	H
314	H		OH	H	H
315	H		OH	H	H
316	H		OH	H	H
317	H		OH	H	H
318	H		OH	H	H

Table-3(continued)

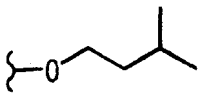
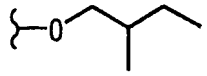
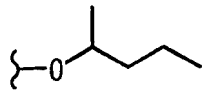
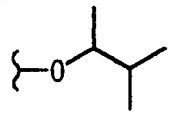
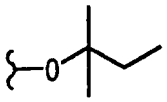
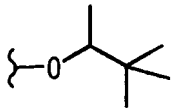
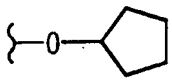
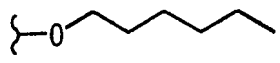
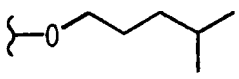
Compound No.	X^1	X^2	X^3	X^4	X^5
319	H		OH	H	H
320	H		OH	H	H
321	H		OH	H	H
322	H		OH	H	H
323	H		OH	H	H
324	H		OH	H	H
325	H		OH	H	H
326	H		OH	H	H
327	H		OH	H	H

Table-3(continued)

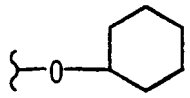
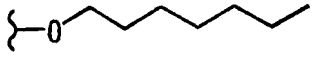
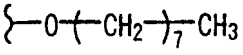
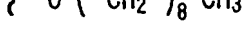
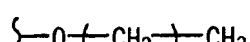
Compound No.	X^1	X^2	X^3	X^4	X^5
328	H		OH	H	H
329	H		OH	H	H
330	H		OH	H	H
331	H		OH	H	H
332	H		OH	H	H
333	H		OH	H	H
334	H		OH	H	H
335	H		OH	H	H
336	H		OH	H	H

Table-3(continued)

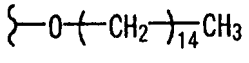
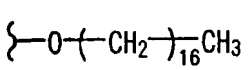
Compound No.	X^1	X^2	X^3	X^4	X^5
337	H		OH	H	H
338	H		OH	H	H
339	H		OH	H	H
340	H		OH	H	H

Table-3(continued)

Compound No.	X^1	X^2	X^3	X^4	X^5
341	OH	H	H	H	H
342	H	OH	H	H	H
343	H	H	OH	H	H
344	H	OH	OH	H	H
345	H	OH	H	OH	H
346	OMe	H	H	H	H
347	H	OMe	H	H	H
348	H	H	OMe	H	H
349	H	OMe	OMe	H	H
350	H	OMe	H	OMe	H
351	H	OH	OMe	H	H
352	H	OMe	OH	Br	H
353	O^{i}Pr	H	H	H	H
354	COOH	H	H	H	H
355	COOMe	H	H	H	H
356	$CONH_2$	H	H	H	H
357	Me	H	H	H	H
358	H	Me	H	H	H
359	H	H	Me	H	H

Table-3(continued)

Compound No.	X^1	X^2	X^3	X^4	X^5
360	H	Me	H	Me	H
361	H	Me	OH	H	H
362	H	Me	OMe	H	H
363	H	Pr	OH	H	H
364	H	Pr	OMe	H	H
365	F	H	H	H	H
366	H	F	H	H	H
367	H	H	F	H	H
368	F	F	H	H	H
369	Cl	H	H	H	H
370	H	Cl	H	H	H
371	H	H	Cl	H	H
372	H	Cl	Cl	H	H
373	Br	H	H	H	H
374	H	Br	H	H	H
375	H	H	Br	H	H
376	H	Br	Br	H	H
377	H	Br	OH	H	H
378	NH_2	H	H	H	H

Table-3(continued)

Compound No.	X^1	X^2	X^3	X^4	X^5
379	H	NH_2	H	H	H
380	H	H	NH_2	H	H
381	NH_2	OMe	H	H	H
382	H	NH_2	OMe	H	H
383	H	NH_2	OH	H	H
384	H	OMe	NH_2	H	H
385	H	OH	NH_2	H	H
386	NO_2	H	H	H	H
387	H	NO_2	H	H	H
388	H	H	NO_2	H	H
389	NO_2	OMe	H	H	H
390	NO_2	OH	H	H	H
391	NO_2	Me	H	H	H
392	NO_2	H	OMe	OMe	H
393	NO_2	Cl	H	H	H
394	H	NO_2	OMe	H	H
395	H	NO_2	OH	H	H
396	H	OMe	NO_2	H	H
397	H	OH	NO_2	H	H

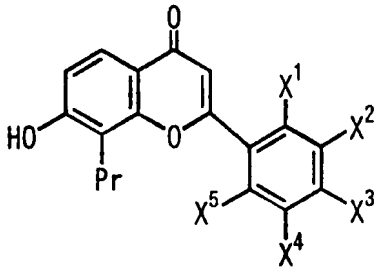


Table-4

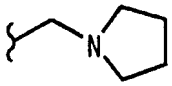
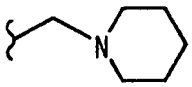
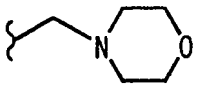
Compound No.	X^1	X^2	X^3	X^4	X^5
398		H	H	H	H
399		H	H	H	H
400		H	H	H	H
401		H	H	H	H
402		H	H	H	H
403		H	H	H	H
404		H	H	H	H

Table-4(continued)

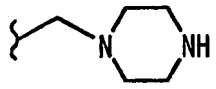
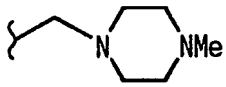
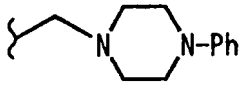
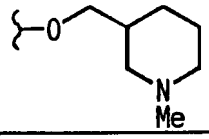
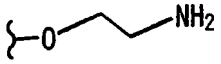
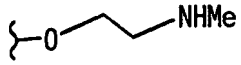
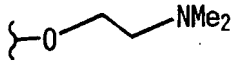
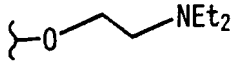
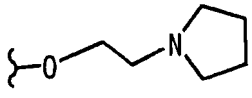
Compound No.	X^1	X^2	X^3	X^4	X^5
405		H	H	H	H
406		H	H	H	H
407		H	H	H	H
408		H	H	H	H
409		H	H	H	H
410		H	H	H	H
411		H	H	H	H
412		H	H	H	H
413		H	H	H	H

Table-4(continued)

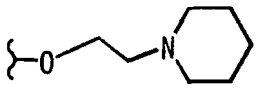
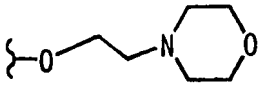
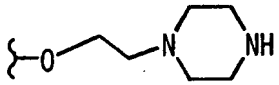
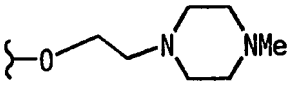
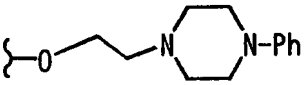
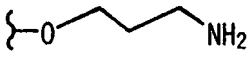
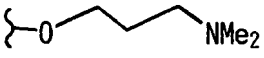
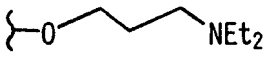
Compound No.	X^1	X^2	X^3	X^4	X^5
414		H	H	H	H
415		H	H	H	H
416		H	H	H	H
417		H	H	H	H
418		H	H	H	H
419		H	H	H	H
420		H	H	H	H
421		H	H	H	H
422		H	H	H	H

Table-4(continued)

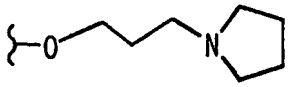
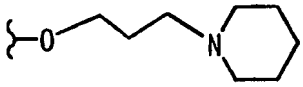
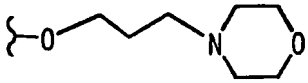
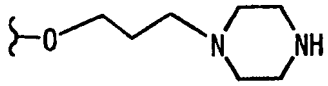
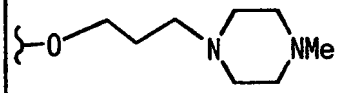
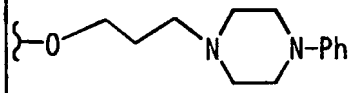
Compound No.	X^1	X^2	X^3	X^4	X^5
423		H	H	H	H
424		H	H	H	H
425		H	H	H	H
426		H	H	H	H
427		H	H	H	H
428		H	H	H	H

Table-4(continued)

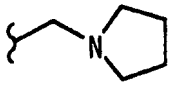
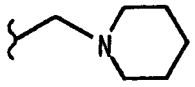
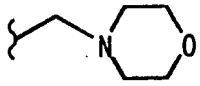
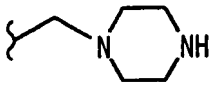
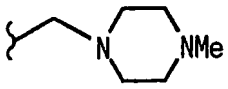
Compound No.	X^1	X^2	X^3	X^4	X^5
429	H		H	H	H
430	H		H	H	H
431	H		H	H	H
432	H		H	H	H
433	H		H	H	H
434	H		H	H	H
435	H		H	H	H
436	H		H	H	H
437	H		H	H	H

Table-4(continued)

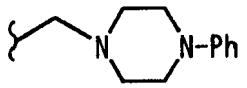
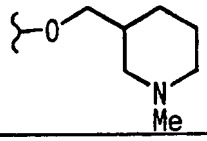
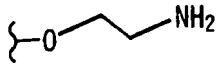
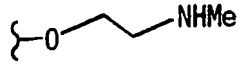
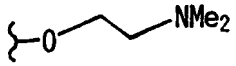
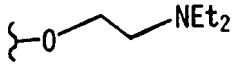
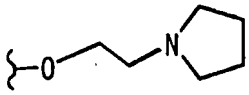
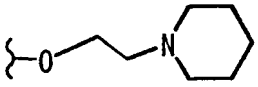
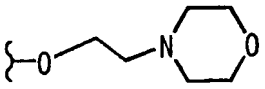
Compound No.	X^1	X^2	X^3	X^4	X^5
438	H		H	H	H
439	H		H	H	H
440	H		H	H	H
441	H		H	H	H
442	H		H	H	H
443	H		H	H	H
444	H		H	H	H
445	H		H	H	H
446	H		H	H	H

Table-4(continued)

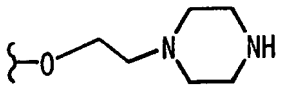
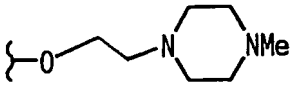
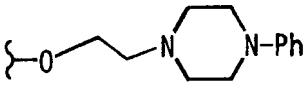
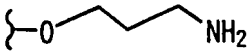
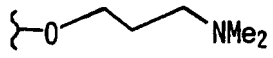
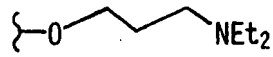
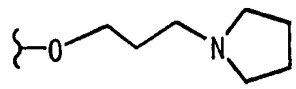
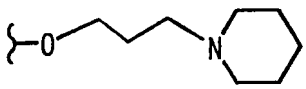
Compound No.	X^1	X^2	X^3	X^4	X^5
447	H		H	H	H
448	H		H	H	H
449	H		H	H	H
450	H		H	H	H
451	H		H	H	H
452	H		H	H	H
453	H		H	H	H
454	H		H	H	H
455	H		H	H	H

Table-4(continued)

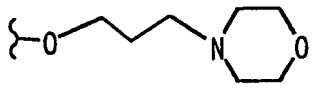
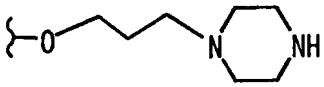
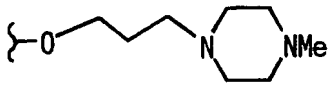
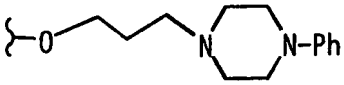
Compound No.	X^1	X^2	X^3	X^4	X^5
456	H		H	H	H
457	H		H	H	H
458	H		H	H	H
459	H		H	H	H

Table-4(continued)

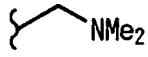
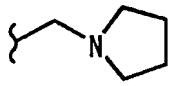
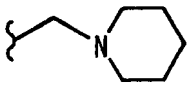
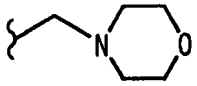
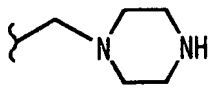
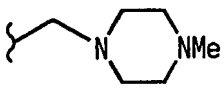
Compound No.	X^1	X^2	X^3	X^4	X^5
460	H	H		H	H
461	H	H		H	H
462	H	H		H	H
463	H	H		H	H
464	H	H		H	H
465	H	H		H	H
466	H	H		H	H
467	H	H		H	H
468	H	H		H	H

Table-4(continued)

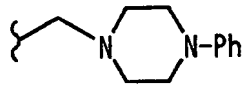
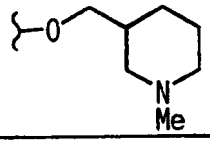
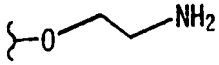
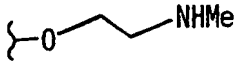
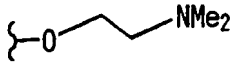
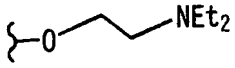
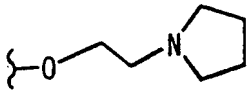
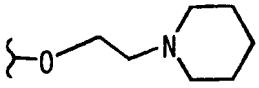
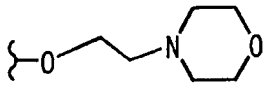
Compound No.	X^1	X^2	X^3	X^4	X^5
469	H	H		H	H
470	H	H		H	H
471	H	H		H	H
472	H	H		H	H
473	H	H		H	H
474	H	H		H	H
475	H	H		H	H
476	H	H		H	H
477	H	H		H	H

Table-4(continued)

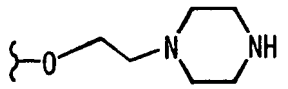
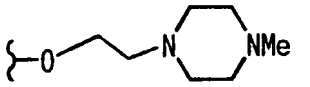
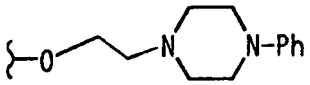
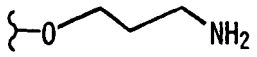
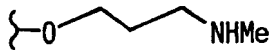
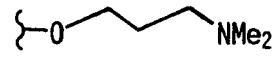
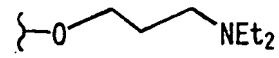
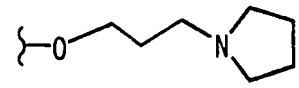
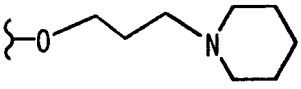
Compound No.	X^1	X^2	X^3	X^4	X^7
478	H	H		H	H
479	H	H		H	H
480	H	H		H	H
481	H	H		H	H
482	H	H		H	H
483	H	H		H	H
484	H	H		H	H
485	H	H		H	H
486	H	H		H	H

Table-4(continued)

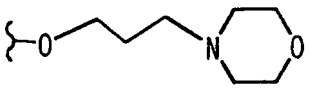
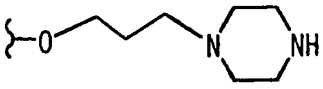
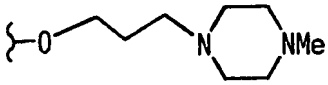
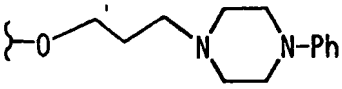
Compound No.	X^1	X^2	X^3	X^4	X^5
487	H	H		H	H
488	H	H		H	H
489	H	H		H	H
490	H	H		H	H

Table-4(continued)

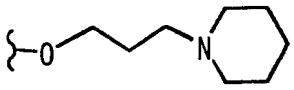
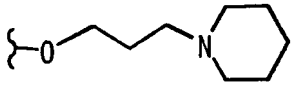
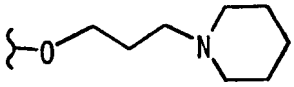
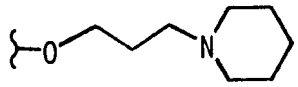
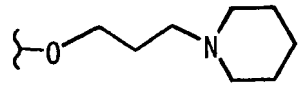
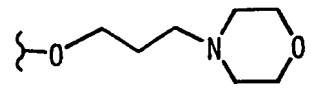
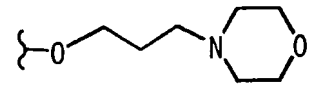
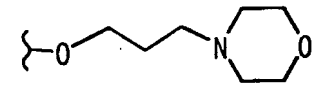
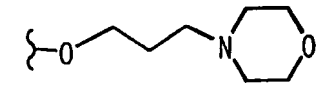
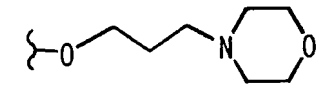
Compound No.	X^1	X^2	X^3	X^4	X^5
491	H		NO_2	H	H
492	H		NH_2	H	H
493	H		OMe	H	H
494	H		H	OMe	H
495	H		H	OH	H
496	H		NO_2	H	H
497	H		NH_2	H	H
498	H		OMe	H	H
499	H		H	OMe	H
500	H		H	OH	H

Table-4(continued)

Compound No.	X^1	X^2	X^3	X^4	X^5
501	OH	H	H	H	H
502	H	OH	H	H	H
503	H	H	OH	H	H
504	H	OH	OH	H	H
505	H	OH	H	OH	H
506	OMe	H	H	H	H
507	H	OMe	H	H	H
508	H	H	OMe	H	H
509	H	OMe	OMe	H	H
510	H	OMe	H	OMe	H
511	H	OH	OMe	H	H
512	H	OMe	OH	Br	H
513	O^iPr	H	H	H	H
514	COOH	H	H	H	H
515	COOMe	H	H	H	H
516	$CONH_2$	H	H	H	H
517	Me	H	H	H	H
518	H	Me	H	H	H
519	H	H	Me	H	H

Table-4(continued)

Compound No.	X^1	X^2	X^3	X^4	X^5
520	H	Me	H	Me	H
521	H	Me	OH	H	H
522	H	Me	OMe	H	H
523	H	Pr	OH	H	H
524	H	Pr	OMe	H	H
525	F	H	H	H	H
526	H	F	H	H	H
527	H	H	F	H	H
528	F	F	H	H	H
529	Cl	H	H	H	H
530	H	Cl	H	H	H
531	H	H	Cl	H	H
532	H	Cl	Cl	H	H
533	Br	H	H	H	H
534	H	Br	H	H	H
535	H	H	Br	H	H
536	H	Br	OH	H	H
537	NH_2	H	H	H	H
538	H	NH_2	H	H	H

Table-4(continued)

Compound No.	X^1	X^2	X^3	X^4	X^5
539	H	H	NH_2	H	H
540	NH_2	OMe	H	H	H
541	H	NH_2	OMe	H	H
542	H	NH_2	OH	H	H
543	H	OMe	NH_2	H	H
544	H	OH	NH_2	H	H
545	NO_2	H	H	H	H
546	H	NO_2	H	H	H
547	H	H	NO_2	H	H
548	NO_2	OMe	H	H	H
549	NO_2	OH	H	H	H
550	NO_2	Me	H	H	H
551	NO_2	H	OMe	OMe	H
552	NO_2	Cl	H	H	H
553	H	NO_2	OMe	H	H
554	H	NO_2	OH	H	H
555	H	OMe	NO_2	H	H
556	H	OH	NO_2	H	H
557	H	H	H	H	H
558	H	O-Ph	H	H	H

Table-4(continued)

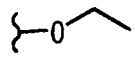
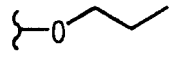
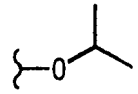
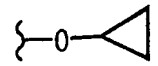
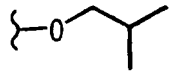
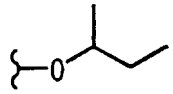
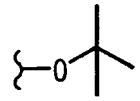
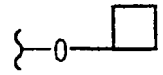
Compound No.	X^1	X^2	X^3	X^4	X^5
559	H		OH	H	H
560	H		OH	H	H
561	H		OH	H	H
562	H		OH	H	H
563	H		OH	H	H
564	H		OH	H	H
565	H		OH	H	H
566	H		OH	H	H
567	H		OH	H	H

Table-4(continued)

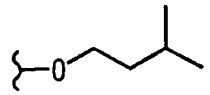
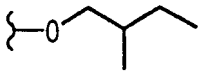
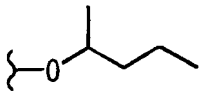
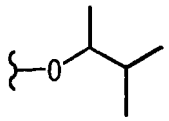
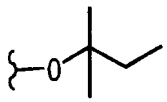
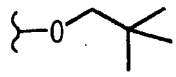
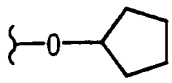
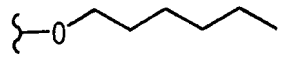
Compound No.	X^1	X^2	X^3	X^4	X^5
568	H		OH	H	H
569	H		OH	H	H
570	H		OH	H	H
571	H		OH	H	H
572	H		OH	H	H
573	H		OH	H	H
574	H		OH	H	H
575	H		OH	H	H
576	H		OH	H	H

Table-4(continued)

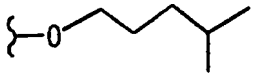
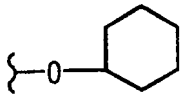
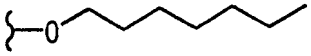
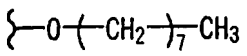
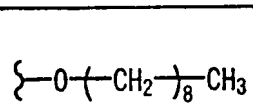
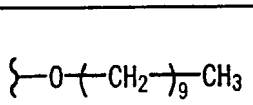
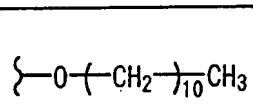
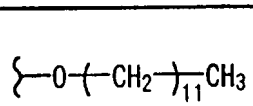
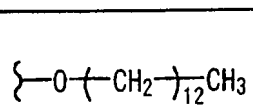
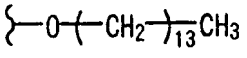
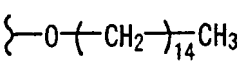
Compound No.	X^1	X^2	X^3	X^4	X^5
577	H		OH	H	H
578	H		OH	H	H
579	H		OH	H	H
580	H		OH	H	H
581	H		OH	H	H
582	H		OH	H	H
583	H		OH	H	H
584	H		OH	H	H
585	H		OH	H	H

Table-4(continued)

Compound No.	X^1	X^2	X^3	X^4	X^5
586	H		OH	H	H
587	H		OH	H	H
588	H		OH	H	H
589	H		OH	H	H
590	H		OH	H	H

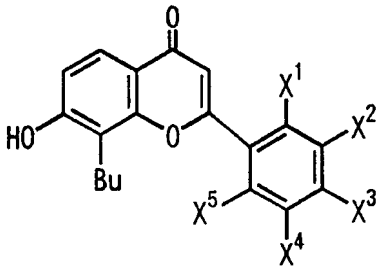


Table-5

Compound No.	X^1	X^2	X^3	X^4	X^5
591	OH	H	H	H	H
592	H	OH	H	H	H
593	H	H	OH	H	H
594	H	OH	OH	H	H
595	H	OH	H	OH	H
596	OMe	H	H	H	H
597	H	OMe	H	H	H
598	H	H	OMe	H	H
599	H	OMe	OMe	H	H
600	H	OMe	H	OMe	H
601	H	OH	OMe	H	H
602	H	OMe	OH	Br	H
603	O^iPr	H	H	H	H
604	COOH	H	H	H	H

Table-5(continued)

Compound No.	X^1	X^2	X^3	X^4	X^5
605	COOMe	H	H	H	H
606	$CONH_2$	H	H	H	H
607	Me	H	H	H	H
608	H	Me	H	H	H
609	H	H	Me	H	H
610	H	Me	H	Me	H
611	H	Me	OH	H	H
612	H	Me	OMe	H	H
613	H	Pr	OH	H	H
614	H	Pr	OMe	H	H
615	F	H	H	H	H
616	H	F	H	H	H
617	H	H	F	H	H
618	F	F	H	H	H
619	Cl	H	H	H	H
620	H	Cl	H	H	H
621	H	H	Cl	H	H
622	H	Cl	Cl	H	H
623	Br	H	H	H	H
624	H	Br	H	H	H

Table-5(continued)

Compound No.	X^1	X^2	X^3	X^4	X^5
625	H	H	Br	H	H
626	H	Br	Br	H	H
627	H	Br	OH	H	H
628	NH_2	H	H	H	H
629	H	NH_2	H	H	H
630	H	H	NH_2	H	H
631	NH_2	OMe	H	H	H
632	H	NH_2	OMe	H	H
633	H	NH_2	OH	H	H
634	H	OMe	NH_2	H	H
635	H	OH	NH_2	H	H
636	NO_2	H	H	H	H
637	H	NO_2	H	H	H
638	H	H	NO_2	H	H
639	NO_2	OMe	H	H	H
640	NO_2	OH	H	H	H
641	NO_2	Me	H	H	H
642	NO_2	H	OMe	OMe	H
643	NO_2	Cl	H	H	H
644	H	NO_2	OMe	H	H

Table-5(continued)

Compound No.	X^1	X^2	X^3	X^4	X^5
645	H	NO_2	OH	H	H
646	H	OMe	NO_2	H	H
647	H	OH	NO_2	H	H
648	H	H	H	H	H

Table-5(continued)

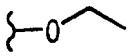
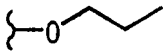
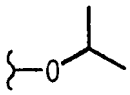
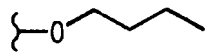
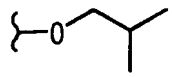
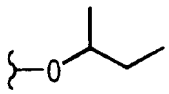
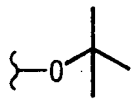
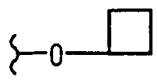
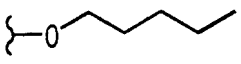
Compound No.	X^1	X^2	X^3	X^4	X^5
649	H		OH	H	H
650	H		OH	H	H
651	H		OH	H	H
652	H		OH	H	H
653	H		OH	H	H
654	H		OH	H	H
655	H		OH	H	H
656	H		OH	H	H
657	H		OH	H	H

Table-5(continued)

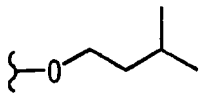
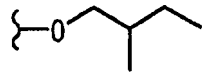
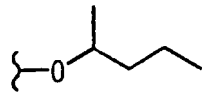
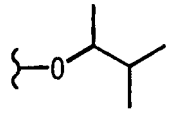
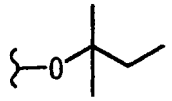
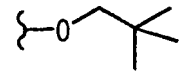
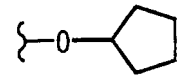
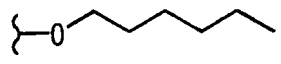
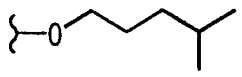
Compound No.	X^1	X^2	X^3	X^4	X^5
658	H		OH	H	H
659	H		OH	H	H
660	H		OH	H	H
661	H		OH	H	H
662	H		OH	H	H
663	H		OH	H	H
664	H		OH	H	H
665	H		OH	H	H
666	H		OH	H	H

Table-5(continued)

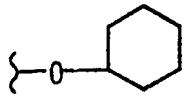
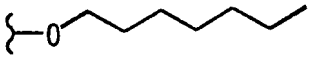
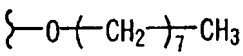
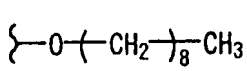
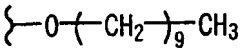
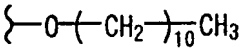
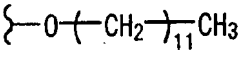
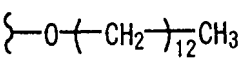
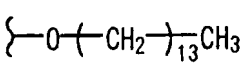
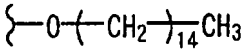
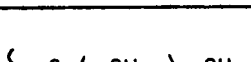
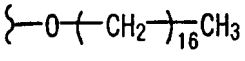
Compound No.	X^1	X^2	X^3	X^4	X^5
667	H		OH	H	H
668	H		OH	H	H
669	H		OH	H	H
670	H		OH	H	H
671	H		OH	H	H
672	H		OH	H	H
673	H		OH	H	H
674	H		OH	H	H
675	H		OH	H	H

Table-5(continued)

Compound No.	X^1	X^2	X^3	X^4	X^5
676	H		OH	H	H
677	H		OH	H	H
678	H		OH	H	H
679	H		OH	H	H

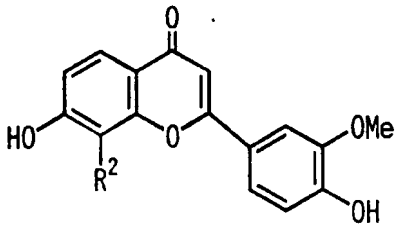


Table-6

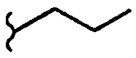
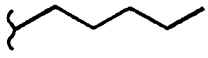
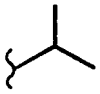
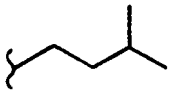
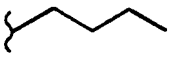
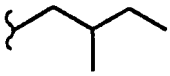
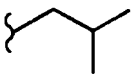
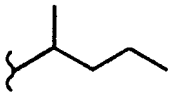
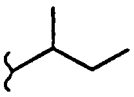
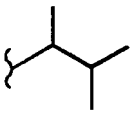
Compound No.	R^2	Compound No.	R^2
680		687	
681		688	
682		689	
683		690	
684		691	
685		692	
686		693	

Table-6(continued)

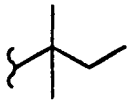
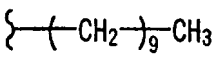
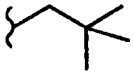
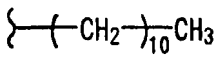
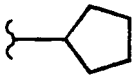
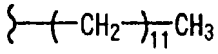
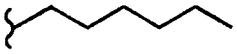
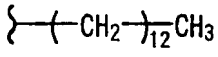
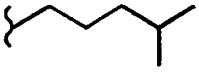
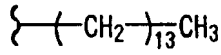
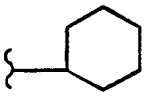
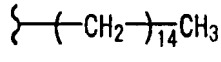
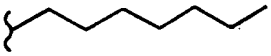
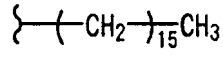
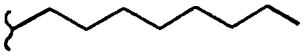
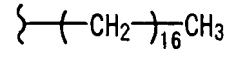
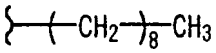
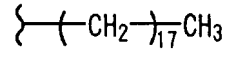
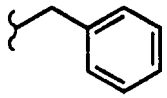
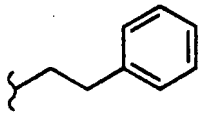
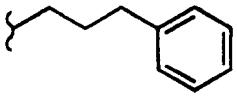
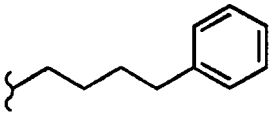
Compound No.	R^2	Compound No.	R^2
694		703	
695		704	
696		705	
697		706	
698		707	
699		708	
700		709	
701		710	
702		711	

Table-6(continued)

Compound No.	R^2
712	
713	
714	
715	

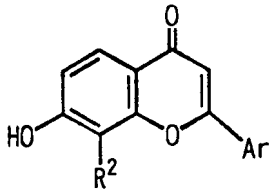


Table-7

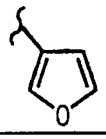
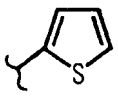
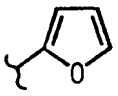
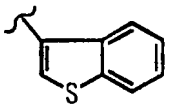
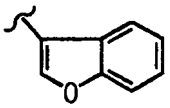
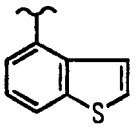
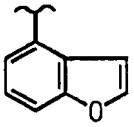
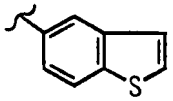
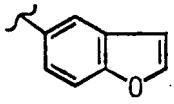
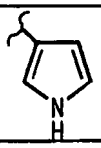
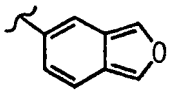
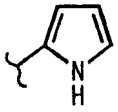
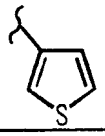
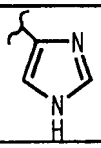
Compound No.	R^2	Ar	Compound No.	R^2	Ar
716	Me		723	Me	
717	Me		724	Me	
718	Me		725	Me	
719	Me		726	Me	
720	Me		727	Me	
721	Me		728	Me	
722	Me		729	Me	

Table-7(continued)

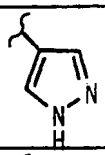
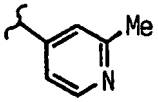
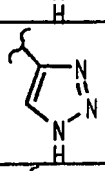
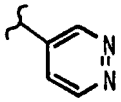
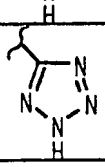
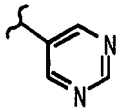
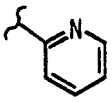
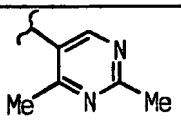
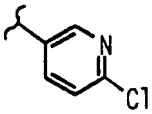
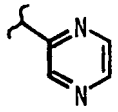
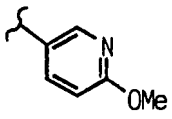
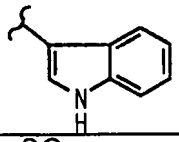
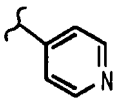
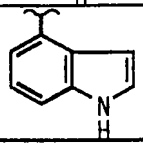
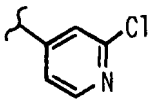
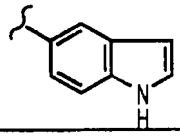
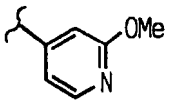
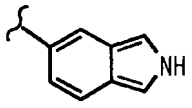
Compound No.	R^2	Ar	Compound No.	R^2	Ar
730	Me		739	Me	
731	Me		740	Me	
732	Me		741	Me	
733	Me		742	Me	
734	Me		743	Me	
735	Me		744	Me	
736	Me		745	Me	
737	Me		746	Me	
738	Me		747	Me	

Table-7(continued)

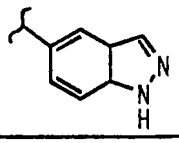
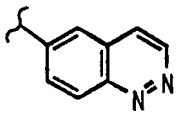
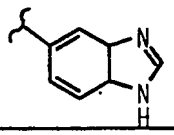
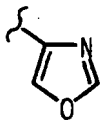
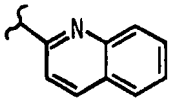
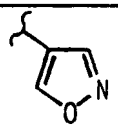
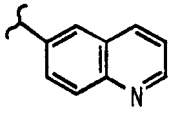
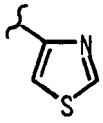
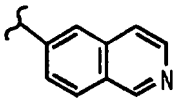
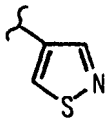
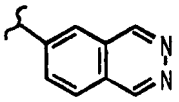
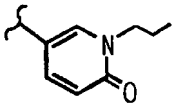
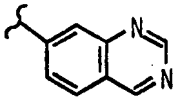
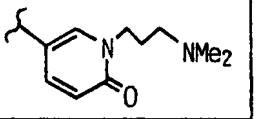
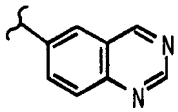
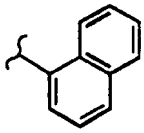
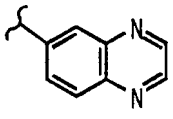
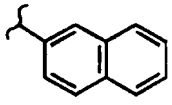
Compound No.	R^2	Ar	Compound No.	R^2	Ar
748	Me		757	Me	
749	Me		758	Me	
750	Me		759	Me	
751	Me		760	Me	
752	Me		761	Me	
753	Me		762	Me	
754	Me		763	Me	
755	Me		764	Me	
756	Me		765	Me	

Table-7(continued)

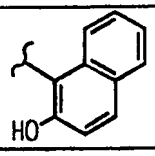
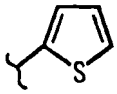
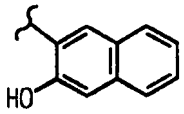
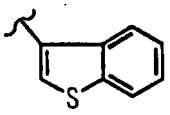
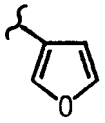
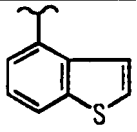
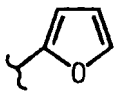
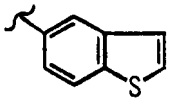
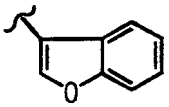
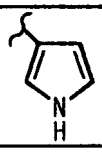
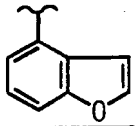
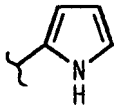
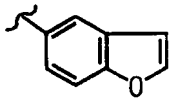
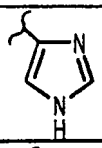
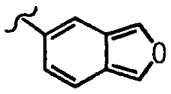
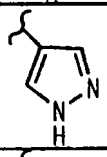
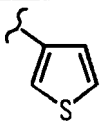
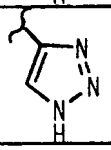
Compound No.	R^2	Ar	Compound No.	R^2	Ar
766	Me		775	Pr	
767	Me		776	Pr	
768	Pr		777	Pr	
769	Pr		778	Pr	
770	Pr		779	Pr	
771	Pr		780	Pr	
772	Pr		781	Pr	
773	Pr		782	Pr	
774	Pr		783	Pr	

Table-7(continued)

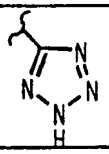
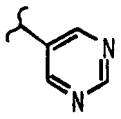
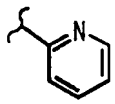
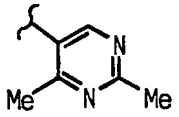
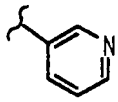
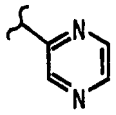
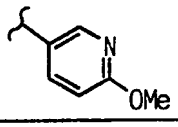
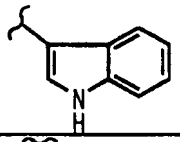
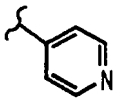
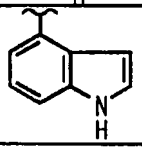
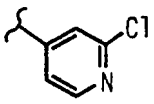
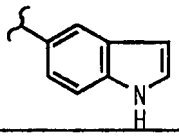
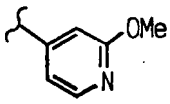
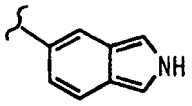
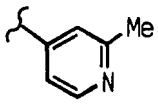
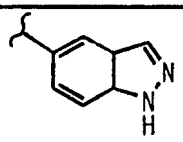
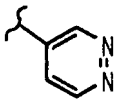
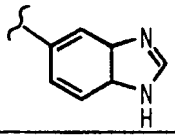
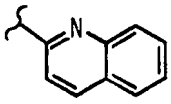
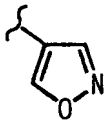
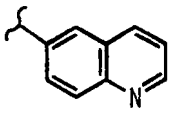
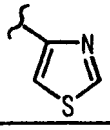
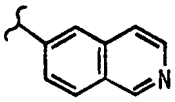
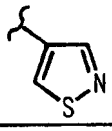
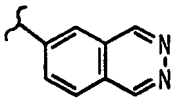
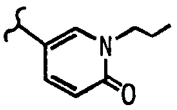
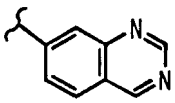
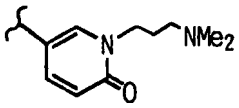
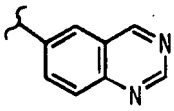
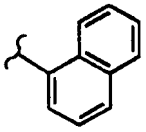
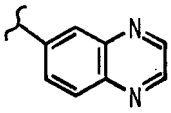
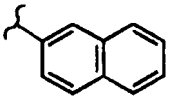
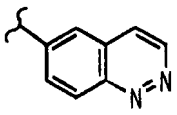
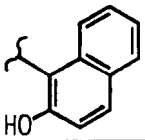
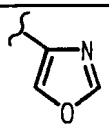
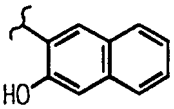
Compound No.	R^2	Ar	Compound No.	R^2	Ar
784	Pr		793	Pr	
785	Pr		794	Pr	
786	Pr		795	Pr	
787	Pr		796	Pr	
788	Pr		797	Pr	
789	Pr		798	Pr	
790	Pr		799	Pr	
791	Pr		800	Pr	
792	Pr		801	Pr	

Table-7(continued)

Compound No.	R^2	Ar	Compound No.	R^2	Ar
802	Pr		811	Pr	
803	Pr		812	Pr	
804	Pr		813	Pr	
805	Pr		814	Pr	
806	Pr		815	Pr	
807	Pr		816	Pr	
808	Pr		817	Pr	
809	Pr		818	Pr	
810	pr		819	Pr	

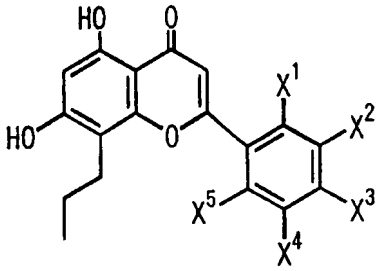


Table-8

Compound No.	X^1	X^2	X^3	X^4	X^5
820	H	H	H	H	H
821	Me	H	H	H	H
822	H	Me	H	H	H
823	H	H	Me	H	H
824	OMe	H	H	H	H
825	H	OMe	H	H	H
826	H	H	OMe	H	H
827	OH	H	H	H	H
828	H	OH	H	H	H
829	H	H	OH	H	H
830	H	OH	OH	H	H
831	H	OH	OMe	H	H
832	H	OMe	OH	H	H
833	H	OEt	OH	H	H

Table-8(continued)

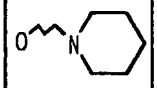
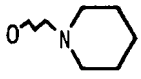
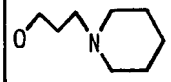
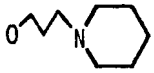
Compound No.	X^1	X^2	X^3	X^4	X^5
834	H	OPr	OH	H	H
835	H	O^{i}Pr	OH	H	H
836	H	OBu	OH	H	H
837	F	H	H	H	H
838	H	F	H	H	H
839	H	H	F	H	H
840	F	F	H	H	H
841	NO_2	H	H	H	H
842	H	NO_2	H	H	H
843	H	H	NO_2	H	H
844	NO_2	Cl	H	H	H
845	NO_2	OMe	H	H	H
846	NO_2	OH	H	H	H
847	NO_2	Me	H	H	H
848	NO_2	H	OMe	OMe	H
849		H	H	H	H
850	H		H	H	H

Table-8(continued)

Compound No.	X^1	X^2	X^3	X^4	X^5
851	H	H		H	H
852	H		NO_2	H	H
853	H	H	NH_2	H	H
854	H	H	OMe	H	H
855	H	H	OH	H	H
856	H		H	H	H

Among the compounds represented by the formula (I), particularly preferred compounds as the active ingredient of the medicament of the present invention include:

(1) those wherein R^1 is hydrogen atom;

(2) those wherein R^2 is hydrogen atom or a C_1-C_{18} alkyl group;

(3) those wherein R^2 is a C_1-C_{18} alkyl group;

(4) those wherein R^2 is a C_2-C_{18} alkyl group;

(5) those wherein Ar is a substituted phenyl group, a C_{10}-C_{14} aryl group which may be substituted, or an aromatic heterocyclic group which may be substituted;

(6) those wherein Ar is a substituted C_6-C_{14} aryl group or an aromatic heterocyclic group which may be substituted;

(7) those wherein Ar is a substituted C_6-C_{14} aryl group;

(8) those wherein Ar is a group represented by the aforementioned formula (II);

(9) those wherein R^2 is a C_1-C_{18} alkyl group which may have one or more C_6-C_{14} aryl groups, and Ar is a C_6-C_{14} aryl group which may be substituted, or an aromatic heterocyclic group which may be substituted;

(10) those wherein R^2 is a C_1-C_{18} alkyl group which may have one or more C_6-C_{14} aryl groups, and Ar is a substituted phenyl group, a C_{10}-C_{14} aryl group which may be substituted, or an aromatic heterocyclic group which may be substituted;

(11) those wherein R^2 is a C_1-C_{18} alkyl group which may have one or more C_6-C_{14} aryl groups, and Ar is a substituted C_6-C_{14} aryl group;

(12) the compounds of the above (9) to (11) wherein R^1 is hydrogen atom;

(13) the compounds of the above (9) to (12) wherein Ar is a group represented by the aforementioned formula (II);

(14) the compounds of the above (9) to (13) wherein R^2 is a C_1-C_{18} alkyl group;

(15) the compounds of the above (9) to (13) wherein R^2 is a C_2-C_{18} alkyl group; and

(16) the compounds of the above (9) to (12) wherein R^2 is a C_4-C_{18} alkyl group.

In addition, particularly preferred compounds also include:

(17) the hydroxyflavone derivatives according to formula (IV) wherein n is 2 or 3;

(18) the hydroxyflavone derivative according to formula (IV) wherein R^5 is hydrogen atom or methoxy group;

(19) the hydroxyflavone derivative according to formula (IV) wherein Z is dimethylamino group, piperazinyl group which may be substituted, or piperidinyl group which may be substituted;

(20) the hydroxyflavone derivative according to formula (V) wherein R^4 is a C_1-C_{18} alkyl group which may be substituted, a C_1-C_{18} alkoxyl group which may be substituted, hydroxyl group, nitro group, or a cyano group;

(21) the hydroxyflavone derivative according to formula (I) wherein R^1 represents hydrogen atom or hydroxyl group; R^2 represents hydrogen atom or a C_1-C_{18} alkyl group which may have one or more C_6-C_{14} aryl groups; and Ar represents an aromatic heterocyclic group which may be substituted, provided that those wherein R^1 is hydrogen atom; R^2 is methyl group, and Ar is a pyridyl group are excluded.

Most preferred compound include:

7-hydroxy-3'-(3-(1-piperidyl)propyloxy)-8-propylflavone.

4',7-dihydroxy-3'-methoxy-8-propylflavone,

7-hydroxy-8-methyl-3'-(3-(1-piperidyl)propyloxy)flavone.

7-hydroxy-4'-nitro-3'-(3-(1-piperidyl)propyloxy)-8-propylflavone,

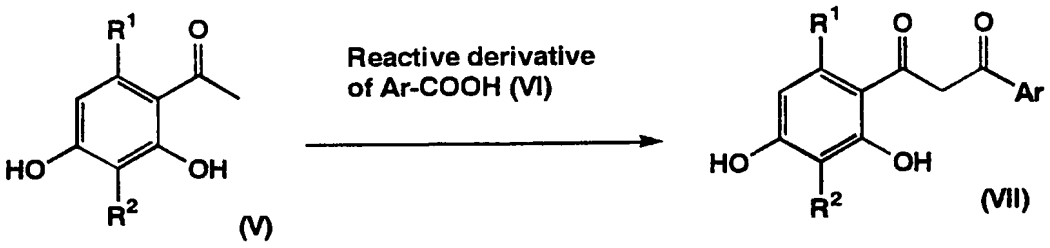
4',7-dihydroxy-3'-methoxy-8-methylflavone, and

7-hydroxy-8-propyl-2-(4-pyridyl)chromone.

However, the active ingredient of the medicament of the present invention is not limited to the compounds specifically mentioned above.

The hydroxyflavone derivatives represented by the aforementioned formula (I) can be prepared by a method described in the literature. For example, they can be prepared as follows.

<Step 1>

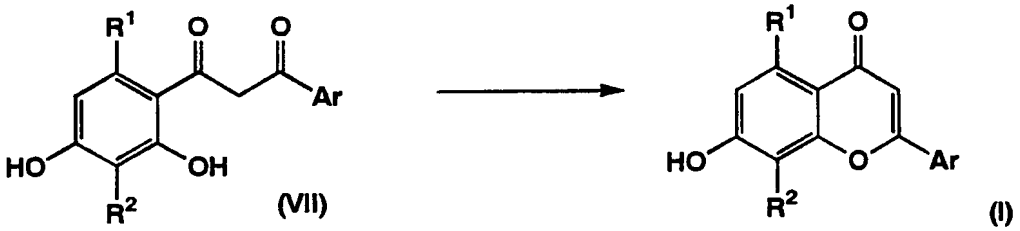


(The symbols used in the scheme have the same meanings as those defined above.)

A compound represented by the aforementioned formula (VII) can be obtained by allowing a compound represented by the aforementioned formula (V) to react with a base and a reactive derivative represented by the aforementioned formula (VI) in the presence of a solvent. The type of the solvent is not particularly limited so long as it does not affect the reaction. For example, ethers such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether and dioxane, aromatic hydrocarbons such as benzene, toluene, and xylene, halogenated hydrocarbons such as dichloromethane, chloroform, and dichloroethane can be used as a solvent.

Two or more of the solvents may be used in combination. Examples of the base include, for example, methyllithium, butyllithium, lithium hexamethyldisilazane, sodium hexamethyldisilazane, lithium diisopropylamide, sodium hydroxide, potassium hydroxide, sodium hydride and the like. As the reactive derivative represented by the formula (VI), symmetric acid anhydrides, mixed acid anhydrides, acid halides, active amides, esters and the like can be used, and these compounds can be readily prepared from corresponding carboxylic acids by a method described in the literature. Reaction temperature and reaction time are not particularly limited. Normally, the reaction can be performed at a temperature of from -78°C to 250°C for 30 minutes to 48 hours.

<Step 2>



(The symbols used in the scheme have the same meanings as those defined above.)

The compound represented by the formula (VII) obtained in Step 1 can be subjected to dehydration reaction in the presence or absence of a solvent to obtain a compound represented by the formula (I). The type of the solvent is not particularly limited so long as it does not affect the reaction. For example, ethers such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether and dioxane, aromatic hydrocarbons such as benzene, toluene, and xylene, halogenated hydrocarbons such as

dichloromethane, chloroform, and dichloroethane. nitriles such as acetonitrile and propionitrile, esters such as methyl acetate and ethyl acetate, alcohols such as methanol and ethanol, organic acids such as acetic acid, acid anhydrides such as acetic anhydride and the like can be used. Two or more of these solvents may be used in combination. The aforementioned dehydration reaction can be performed in the presence of acid catalyst. Examples of the acid catalyst include, for example, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid, and organic acids such as trifluoroacetic acid, p-toluenesulfonic acid, methanesulfonic acid, and camphorsulfonic acid and the like. Reaction temperature and reaction time are not particularly limited. Normally, the reaction can usually be performed at a temperature of from 0°C to 250°C for 30 minutes to 48 hours. In each of the aforementioned steps, protection of functional groups and deprotection may sometimes be required. Protective groups can be chosen so as to be suitable for such functional groups, and protection and deprotection can be performed in accordance with any methods described in the literature.

The medicament of the present invention have inhibitory activity against TPK1, and they inhibit TPK1 activity in Alzheimer disease and the like, thereby suppress the neurotoxicity of Aβ and the formation of PHF and inhibit the nerve cell death. Accordingly, the medicament of the present invention are useful as a medicament which radically enables preventive and/or therapeutic treatment of Alzheimer disease. In addition, the medicament of the present invention are also useful for preventive and/or therapeutic treatment of ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism,

postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration frontotemporal dementia and the like.

As the active ingredient of the medicament of the present invention, a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The substance, per se, may be administered as the medicament of the present invention, however, it is generally desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more of pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substance may be used in combination. The above pharmaceutical composition may be supplemented with an active ingredient of other medicament for the treatment of Alzheimer disease and the like.

A type of the pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations

such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content rations of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic substances, or solid or liquid substances may be used as pharmaceutical additives. Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1% by weight to 90% by weight based on the weight of an active ingredient.

Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for suppositories include, for example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

Dose and frequency of administration of the medicament of the

present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a disease and the like. Generally, a daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

The hydroxyflavone derivatives represented by the aforementioned formula (I) and salts thereof, and solvates thereof and hydrates thereof are novel substance and fall within the scope of the present invention relating to chemical substances, wherein R^1, R^2, and Ar are the same as those defined above and where R^2 is hydrogen atom, Ar represents a group represented by the aforementioned formula (II) wherein R^3, R^4, R^5, R^6, and R^7 are the same as those defined above, provided that any one of R^3, R^4, R^5, R^6, and R^7 represents a group represented by the aforementioned formula (III) wherein R^8, X, and m are those defined above, provided that those wherein R^1 is hydrogen atom, R^2 is methyl group, and Ar is phenyl group, a 3,4-methylenedioxyphenyl group, or a 3-pyridyl group, those wherein R^1 is hydrogen atom, R^2 is propyl group, and Ar is phenyl group having a carboxyl group or an ester group in the 4-position, and those wherein R^1 is hydroxyl group, R^2 is methyl group, and Ar is phenyl group, 4-hydroxyphenyl group, 4-methoxyphenyl group, or 3,4-dimethoxyphenyl group are excluded.

Utilities of the novel substances provided by the present invention are not limited to medicaments, and any utilities fall within the scope of the

present invention. The substances may exist as stereoisomers such as enantiomers of diastereomers, any pure form of a stereoisomers, any mixture of stereoisomers, racemates also fall within the scope of the present invention. Examples of the substances in the form of salts include physiologically acceptable salts explained above.

Examples

The present invention will be explained more specifically with reference to examples. However, the scope of the present invention is not limited to the following examples. The compound number in the examples corresponds to that in the table above.

Example 1: Preparation of 7-hydroxy-3'-(3-(1-piperidyl)propyloxy)-8-propylflavone disulfate (Compound 455)

2,4-Dihydroxy-3-propylacetophenone (1.0 g) was dissolved in 30 ml of tetrahydrofuran, and the solution was added dropwise with 26 ml of lithium hexamethyldisilazane at -78°C and stirred for 2 hours. A tetrahydrofuran solution of 1.43 g of methyl 3-piperidylpropyloxybenzoate was added dropwise to the reaction mixture, and the mixture was stirred for 24 hours. The reaction mixture was poured into ice-cold water, neutralized with concentrated hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and then concentrated and dried under reduced pressure. The resulting residue was dissolved in 40 ml of acetic acid, added with 0.2 ml of concentrated sulfuric acid, and stirred at 100°C for 2 hours. The reaction mixture was cooled to room temperature, and the deposited solid was separated by filtration and washed with ethyl acetate to obtain 2.69 g of the

desired compound.

Yield: 84%.

Melting point: 233°C.

NMR (DMSO-d_6, δ): 0.98 (t, J=7.5Hz, 3H), 1.41 (m, 1H), 1.63-1.69 (m, 5H), 1.85 (m, 2H), 2.19 (m, 2H), 2.85-2.96 (m, 4H), 3.22 (m, 2H), 3.51 (m, 2H), 4.19 (t, J=6.0Hz, 2H), 6.95 (s, 1H), 7.01 (d, J=8.7Hz, 1H), 7.18 (d, J=8.7Hz, 1H), 7.50-7.56 (m, 2H), 7.66 (d, J=8.0Hz, 1H), 7.77 (d, J=8.7Hz, 1H), 8.99 (br, 1H), 10.60 (br, 1H).

Reference Example 1: Preparation of methyl 4-tert-butyldimethylsiloxy-3-methoxybenzoate

Vanillic acid (25.8 g) was dissolved in 500 ml of methanol, and the solution was added with 1 g of p-toluenesulfonic acid and heated under reflux for 24 hours. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and purified on a column with hexane/ethyl acetate = 3/1 to obtain 28.5 g of methyl vanillate (Yield: 100%). The resulting methyl vanillate (5.5 g) was dissolved in 30ml of N,N-dimethylformamide, and the solution was added with 3.1 g of imidazole and 5.5 g of tert-butyldimethylchlorosilane at 0°C and then stirred at room temperature for 2 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The resulting organic layer was washed with water and saturated brine, dried over sodium sulfate, and then concentrated under reduced pressure. The resulting residue was purified on a column with hexane/ethyl acetate = 15/1 to obtain 8.68 g of the desired compound (Yield: 97%).

NMR ($CDCl_3$, δ): 0.17 (s, 6H), 1.01 (s, 9H), 3.86 (s, 3H), 3.88 (s, 3H), 6.86 (d, J=8.7Hz, 1H), 7.51 (d, J=2.4Hz, 1H), 7.66 (dd, J=8.7Hz, 2.4Hz, 1H).

Example 2: Preparation of 4',7-dihydroxy-3'-methoxy-8-propylflavone (Compound 682)

2,4-Dihydroxy-3-propylacetophenone (1.0 g) was dissolved in 30 ml of tetrahydrofuran, and the solution was added dropwise with 26 ml of lithium hexamethyldisilazane at -78 ℃ and then stirred for 2 hours. A tetrahydrofuran solution of 1.53 g of methyl vanillate obtained in Reference Example 1 was added dropwise to the reaction mixture, and the mixture was stirred for 24 hours. The reaction mixture was poured into ice-cold water, neutralized with concentrated hydrochloric acid, and then extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated and dried under reduced pressure. The resulting residue was dissolved in 40 ml of acetic acid, and the solution was added with 0.2 ml of concentrated sulfuric acid and stirred at 100℃ for 2 hours. The reaction mixture was added with 10 ml of water and further stirred for 2 hours. The reaction mixture was cooled to room temperature, and the deposited solid was separated by filtration and washed with ethyl acetate to obtain 1.47 g of the desired compound.

Yield: 87%.

Melting point: : 231-233℃.

NMR (DMSO-d_6, δ): 0.98 (t, J=7.2Hz, 3H), 1.65 (m, 2H), 2.88 (t, J=6.9Hz, 2H), 3.90 (s, 3H), 6.82 (s, 1H), 6.94-6.99 (m, 2H), 7.51-7.55 (m, 2H), 10.53 (br,1H).

Compounds of Example 3 to 73 were prepared in similar manners to those in Reference Example 1 and Examples 1 and 2. Physical properties of the compounds are shown below.

Example 3: 7-Hydroxy-3'-(1-methyl-3-piperidyl)methoxyflavone (Compound 42)

Melting point: 134℃ (decomposition).

NMR (DMSO-d_6, δ): 1.08 (m, 1H), 1.33 (m, 1H), 1.70 (m, 1H), 1.95 (m, 2H), 2.27 (br, 1H), 2.83 (s, 3H), 3.45 (m, 1H), 3.57 (m, 1H), 3.97 (m, 1H), 4.11 (m, 1H), 6.94-6.97 (m, 2H), 7.01 (s, 1H), 7.17 (d, J=7.2Hz, 1H), 7.5 (m, 1H), 7.57 (s, 1H), 7.67 (d, J=7.5Hz, 1H), 7.89 (d, J=8.7Hz, 1H), 9.26 (br, 1H).

Example 4: 7-Hydroxy-3'-(2-dimethylaminoethoxy)flavone hydrochloride (Compound 45)

Melting point: 238-239℃.

NMR (DMSO-d_6, δ): 2.87 (s, 3H), 2.89 (s, 3H), 4.48 (t, J=5.1Hz, 2H), 6.93-6.98 (m, 2H), 7.03 (d, J=2.1Hz, 1H), 7.23 (dd, J=2.1Hz, 8.1Hz, 1H), 7.53 (t, J=8.1Hz, 1H), 7.65 (d, J=2.1Hz, 1H), 7.71 (d, J=8.1Hz, 1H), 7.89 (d, J=8.7Hz, 1H), 10.10 (br, 1H), 10.90 (br, 1H).

Example 5: 7-Hydroxy-3'-(2-(1-piperidyl)ethoxy)flavone hydrochloride (Compound 48)

Melting point: 120-121℃.

NMR (DMSO-d_6, δ): 1.68-1.83 (m, 4H), 3.03 (m, 2H), 3.51-3.63 (m, 4H), 3.62 (m, 2H), 4.55 (m, 2H), 6.96-6.98 (m, 2H), 7.06 (s, 1H), 7.23 (d, J=8.1Hz, 1H), 7.52 (m, 1H), 7.64 (s, 1H), 7.70 (d, J=7.8Hz, 1H), 7.89 (d, J=8.71H), 10.58 (br, 1H).

Example 6: 7-Hydroxy-3'-(3-dimethylaminopropyloxy)flavone hydrochloride (Compound 55)

Melting point: 244-245℃.

NMR (DMSO-d_6, δ): 2.18 (m, 2H), 2.80 (s, 3H), 2.81 (s, 3H), 3.25 (m, 2H), 4.19 (t, J=6.0Hz, 2H), 6.93-6.97 (m, 2H), 7.04 (s, 1H), 7.17 (m, 1H), 7.50 (m, 1H), 7.58 (s, 1H), 7.66 (d, J=7.8Hz, 1H), 7.89 (d, J=8.7Hz, 1H), 10.17 (br, 1H), 10.83 (br, 1H).

Example 7: 7-Hydroxy-3'-(3-(1-piperidyl)propyloxy)flavone 1/2sulfate (Compound 58)

Melting point: 205℃ (decomposition).

NMR(DMSO-d_6, δ): 1.42 (m, 1H), 1.59-1.80 (m, 3H), 1.85 (m, 2H), 2.16 (m, 2H), 2.93 (m, 2H), 3.56 (m, 2H), 4.19 (t, J=5.7Hz, 2H), 6.94 (s, 1H), 6.95 (dd, J=2.1Hz, 9.0Hz, 1H), 7.10 (d, J=2.1Hz, 1H), 7.17 (dd, J=2.1Hz, 8.4Hz, 1H), 7.51 (m, 1H), 7.57 (d, J=2.1Hz, 1H), 7.67 (d, J=8.1Hz, 1H), 7.90 (d, J=9.0Hz, 1H), 8.97 (br, 1H), 10.80 (br, 1H).

Example 8: 7-Hydroxy-3'-(3-(4-phenyl-1-piperazyl)propyloxy)flavone dihydrochloride (Compound 62)

Melting point: 245℃ (decomposition).

NMR (DMSO-d_6, δ): 2.29 (m, 2H), 3.14-3.22 (m, 4H), 3.36 (m, 2H), 3.64 (m, 2H), 3.84 (m, 2H), 6.87 (m, 1H), 6.93-7.05 (m, 5H), 7.18-7.39 (m, 3H), 7.53 (m, 1H), 7.59 (s, 1H), 7.66 (d, J=8.1Hz, 1H), 7.89 (d, J=8.6Hz, 1H), 10.74 (br, 1H).

Example 9: 7-Hydroxy-4'-(3-(1-piperidyl)propyloxy)flavone 1/2sulfate (Compound 89)

Melting point: 210℃.

NMR (DMSO-d_6, δ): 1.41 (m, 1H), 1.58-1.96 (m, 5H), 2.16 (m, 2H), 2.92 (m,

2H), 3.10-3.40 (m, 4H), 3.48 (m, 2H), 4.17 (t, J=6.0Hz, 2H), 6.81 (s, 1H), 6.92 (dd, J=2.1Hz, 9.0Hz, 1H), 6.99 (d, J=2.1Hz, 1H), 7.12 (d, J=8.7Hz, 1H), 7.88 (d, J=8.7Hz, 1H), 8.04 (d, J=9.0Hz, 1H), 9.52 (br, 1H), 9.70 (br, 1H), 10.76 (s, 1H).

Example 10: 7-Hydroxy-4'-methoxy-3'-(3-(1-piperidyl)propyloxy)flavone 1/2sulfate (Compound 96)

Melting point: 210℃ (decomposition).

NMR (DMSO-d_6, δ): 1.42 (m, 1H), 1.58-1.69 (m, 3H), 1.85 (m, 2H), 2.17 (m, 2H), 2.93 (m, 2H), 3.23 (m, 2H), 3.52 (m, 2H), 3.87 (s, 3H), 4.20 (t, J=6.0Hz, 2H), 6.89 (s, 1H), 6.92 (d, J=8.7Hz, 1H), 7.01 (s, 1H), 7.17 (d, J=8.7Hz, 1H), 7.59 (s, 1H), 7.70 (d, J=8.7Hz, 1H), 7.87 (d, J=8.7Hz, 1H), 8.87 (br, 1H).

Example 11: 3',7-Dihydroxy-5'-(3-(1-piperidyl)propyloxy)flavone 1/2sulfate (Compound 98)

Melting point: 180℃.

NMR (DMSO-d_6, δ): 1.40 (m, 1H), 1.62-1.68 (m, 3H), 1.92 (m, 2H), 2.13 (m, 2H), 2.90 (m, 2H), 3.22 (m, 2H), 2.49 (m, 2H), 4.12 (t, J=6.0Hz, 2H), 6.55 (s, 1H), 6.80 (s, 1H), 6.91-6.96 (m, 2H), 7.03 (s, 2H), 7.88 (d, J=8.4Hz, 1H), 8.95 (br, 1H).

Example 12: 5,7-Dihydroxy-3'-(2-dimethylaminoethoxy)flavone (Compound 148)

Melting point: 175-177℃.

NMR (DMSO-d_6, δ): 2.24 (s, 6H), 2.66 (t, J=5.7Hz, 2H), 4.17 (t, J=5.7Hz, 2H), 6.22 (d, J=2.1Hz, 1H), 6.54 (d, J=2.1Hz, 1H), 7.02 (s, 1H), 7.19 (d, J=8.Hz, 1H), 7.48 (t, J=8.1Hz, 1H), 7.59 (s, 1H), 7.64 (d, J=8.1Hz, 1H), 12.82 (s, 1H).

Example 13: 5,7-Dihydroxy-3'-(3-dimethylaminopropyloxy)flavone 1/2sulfate (Compound 158)

Melting point: 220-223℃.

NMR (DMSO-d_6, δ): 2.12 (m, 2H), 2.81 (s, 6H), 3.22 (t, J=8.1Hz, 2H), 4.17 (t, J=6.0Hz, 2H), 6.24 (d, J=2.1Hz, 1H), 6.53 (d, J=2.1Hz, 1H), 7.01 (s, 1H), 7.20 (d, J=7.8Hz, 1H), 7.51 (t, J=7.8Hz, 1H), 7,58 (s, 1H), 7.68 (d, J=7.8Hz, 1H), 12.80 (s, 1H).

Example 14 : 5,7-Dihydroxy-3'-(3-(1-piperidyl)propyloxy)flavone 1/2sulfate (Compound 161)

Melting point: 184-186℃.

NMR (DMSO-d_6, δ): 1.40 (m, 1H), 1.60-1.80 (m, 3H), 1.81-1.93 (m, 2H), 2.49 (m, 2H), 2.94 (m, 2H), 3.46 (m, 2H), 4.18 (t, J=5.7Hz, 2H), 6.24 (d, J=2.1Hz, 1H), 6.53 (d, J=2.1Hz, 1H), 7.01 (s, 1H), 7.19 (d, J=8.1Hz, 1H), 7.51 (d, J=8.1Hz, 1H), 7.57 (s, 1H), 7.68 (d, J=8.1Hz, 1H), 10.93 (s, 1H), 12.80 (s, 1H).

Example 15: 5,7-Dihydroxy-3'-(3-(4-morpholinyl)propyloxy)flavone 1/2sulfate (Compound 162)

Melting point: 210-212℃.

NMR (DMSO-d_6, δ): 2.18 (m, 2H), 3.14 (m, 2H), 3.37 (m, 2H), 3.70 (m, 2H), 4.10 (m, 2H), 4.20 (t, J=6.0Hz, 2H), 6,24 (d, J=2.1Hz, 1H), 6.53 (d, J=2.1Hz, 1H), 7.01 (s, 1H), 7.20 (dd, J=2.1Hz, 8.1Hz, 1H), 7.52 (m, 1H), 7.58 (s, 1H), 7.68 (d, J=7.5Hz, 1H), 9.58 (br, 1H), 10.92 (s, 1H), 12.80 (s, 1H).

Example 16: 7-Hydroxy-8-methyl-3'-(3-(1-piperidyl)propyloxy)flavone

1/2sulfate (Compound 264)

Melting point: 226℃ (decomposition).

NMR (DMSO-d_6, δ): 1.32-1.90 (m, 6H), 2.18 (m, 2H), 2.36 (s, 3H), 2.95 (m, 2H), 3.24 (m, 2H), 3.51 (m, 2H), 4.17 (m, 2H), 6.95 (s, 1H), 7.00 (d, J=8.8Hz, 1H), 7.17 (d, J=7.8Hz, 1H), 7.50-7.57 (m, 2H), 7.69 (d, J=7.8Hz, 1H), 7.76 (d, J=8.8Hz, 1H).

Example 17: 4',7-Dihydroxy-3'-ethoxy-8-methylflavone (Compound 310)

Melting point: 152-156℃.

NMR (DMSO-d_6, δ): 1.37 (t, J=6.9Hz, 3H), 2.83 (s, 3H), 4.15 (q, J=6.9Hz, 2H), 6.79 (s, 1H), 6.95 (d, J=8.8Hz, 2H), 7.52-7.54 (m, 2H), 7.70 (d, J=8.8Hz, 1H).

Example 18: 3',7-Dihydroxy-8-methylflavone (Compound 342)

Melting point: 230-231℃.

NMR (DMSO-d_6, δ): 2.36 (s, 3H), 6.78 (s, 1H), 6.97-7.00 (m, 2H), 7.37 (t, J=7.8Hz, 1H), 7.41-7.51 (m, 2H), 10.61 (s, 1H).

Example 19: 4',7-Dihydroxy-8-methylflavone (Compound 343)

Melting point: >300℃.

NMR (DMSO-d_6, δ): 2.30 (s, 3H), 6.67 (s, 1H), 6.88-6.93 (m, 4H), 7.68 (s, J=7.8Hz, 1H), 7.88 (d, J=8.7Hz, 1H).

Example 20: 7-Hydroxy-3'-methoxy-8-methylflavone (Compound 347)

Melting point: 233-236℃.

NMR (DMSO-d_6, δ): 2.36 (s, 3H), 3.87 (s, 3H), 6.95 (s, 1H), 7.00 (d, J=8.7Hz, 1H), 7.17 (ss, J=2.1Hz, 7.8Hz, 1H), 7.50 (t, J=7.8Hz, 1H), 7.57 (s, 1H), 7.66 (d, J=7.8Hz, 1H), 7.76 (d, J=8.7Hz, 1H), 10.63 (br, 1H).

Example 21: 3',7-Dihydroxy-4'-methoxy-8-methylflavone (Compound 351)

Melting point: 263℃ (decomposition).

NMR (DMSO-d_6, δ): 2.35 (s, 3H), 3.86 (s, 3H), 6.69 (s, 1H), 6.97 (d, J=8.7Hz, 1H), 7.09 (d, J=7.8Hz, 1H), 7.48 (d, J=2.4Hz, 1H), 7.53 (dd, J=2.4Hz, 8.7Hz, 1H), 7.73 (d, J=8.7Hz, 1H), 10.59 (br, 1H).

Example 22: 2'-Carboxy-7-hydroxy-8-methylflavone (Compound 354)

Melting point: >300℃.

NMR (DMSO-d_6, δ): 2.16 (s, 3H), 6.50 (s, 1H), 7.00 (d, J=8.7Hz, 1H), 7.65-7.88 (m, 5H), 10.65 (s, 1H), 13.03 (br, 1H).

Example 23: 2'-Fluoro-7-hydroxy-8-methylflavone (Compound 365)

Melting point: 230-231℃.

NMR (DMSO-d_6, δ): 2.30 (s, 3H), 6.68 (s, 1H), 7.01 (d, J=8.7Hz, 1H), 7.42-7.49 (m, 2H), 7.65 (m, 1H), 7.77 (d, J=8.7Hz, 1H), 8.02 (m, 1H), 10.68 (br, 1H).

Example 24: 2',3'-Difluoro-7-hydroxy-8-methylflavone (Compound 368)

Melting point: 229℃.

NMR (DMSO-d_6, δ): 2.29 (s, 3H), 6.71 (s, 1H), 7.02 (d, J=8.4Hz, 1H), 7.45 (m, 1H), 7.60-7.90 (m, 3H), 10.70 (br, 1H).

Example 25: 7-Hydroxy-8-methyl-2'-nitroflavone (Compound 386)

Melting point: 271-272℃.

NMR (DMSO-d_6, δ): 2.01 (s, 3H), 6.72 (s, 1H), 7.02 (s, J=8.7Hz, 1H), 7.76-8.00 (m, 4H), 8.15 (d, J=7.5Hz, 1H), 10.75 (br, 1H).

Example 26: 7-Hydroxy-8-methyl-3'-nitroflavone (Compound 387)

Melting point: 250℃ (decomposition).

NMR (DMSO-d_6, δ): 2.83 (s, 3H), 7.02 (d, J=8.7Hz, 1H), 7.13 (s, 1H), 7.78 (d, J=8.7Hz, 1H), 7.88 (m, 1H), 8.42 (d, J=7.8Hz, 1H), 8.53 (d, J=8.1Hz, 1H), 8.80 (s, 1H), 10.70 (br, 1H).

Example 27: 7-Hydroxy-3'-methoxy-8-methyl-2'-nitroflavone (Compound 389)

Melting point: 227-229℃.

NMR (DMSO-d_6, δ): 2.11 (s, 3H), 3.87 (s, 3H), 6.67 (s, 1H), 7.01 (d, J=8.7Hz, 1H), 7.54 (d, J=7.8Hz, 1H), 7.61 (d, J=8.7Hz, 1H), 7.72-7.79 (m, 2H), 10.74 (br, 1H).

Example 28: 3',8-Dimethyl-7-hydroxy-2'-nitroflavone (Compound 391)

Melting point: 230℃ (decomposition).

NMR (DMSO-d_6, δ): 2.10 (s, 3H), 2.40 (s, 3H), 6.67 (s, 1H), 7.01 (d, J=8.7Hz, 1H), 7.71-7.82 (m, 4H), 10.78 (br, 1H).

Example 29: 3',4'-Dimethoxy-7-hydroxy-8-methyl-2'-nitroflavone (Compound 392)

Melting point: 284-285℃.

NMR (DMSO-d_6, δ): 2.05 (s, 3H), 3.95 (s, 3H), 3.98 (s, 3H), 6.71 (s, 1H), 7.00 (d, J=8.7Hz, 1H), 7.42 (s, 1H), 7.73 (s, 1H), 7.78 (d, J=8.7Hz, 1H), 10.69 (s,1H).

Example 30: 3'-Chloro-7-hydroxy-8-methyl-2'-nitroflavone (Compound 393)

Melting point: 242-243℃.

NMR (DMSO-d_6, δ): 2.12 (s, 3H), 6.78 (s, 1H), 7.03 (d, J=8.7Hz, 1H), 7.78 (d, J=8.7Hz, 1H), 7.85 (t, J=8.1Hz, 1H), 8.99-8.06 (m, 2H), 10.78 (br, 1H).

Example 31: 7-Hydroxy-4'-nitro-3'-(3-(1-piperidyl)propyloxy)-8-propylflavone 1/2sulfate (Compound 491)

Melting point: 214-217℃.

NMR (DMSO-d_6, δ): 1.97 (t, 3H), 1.65 (m, 6H), 1.84 (m, 2H), 2.21 (m, 2H), 2.91 (m, 4H), 3.21 (m, 2H), 3.48 (m, 2H), 4.43 (m, 2H), 7.03 (d, J=8.7Hz, 1H), 7.20 (s, 1H), 7.79 (d, J=9.0Hz, 2H), 7.90 (s, 1H), 8.14 (d, J=9.0Hz, 1H), 8.95 (br, 1H), 10.69 (br, 1H).

Example 32: 3',7-Dihydroxy-8-propylflavone (Compound 502)

Melting point: 281-282℃.

NMR (DMSO-d_6, δ): 0.97 (t, J=7.5Hz, 3H), 1.64 (m, 2H), 2.88 (t, J=7.5Hz, 2H), 6.78 (s, 1H), 6.99 (d, J=8.7Hz, 1H), 7.38 (t, J=7.8Hz, 1H), 7.40 (s, 1H), 7.48 (d, J=7.8Hz, 1H), 7.76 (s, J=8.7Hz, 1H), 9.88 (s, 1H), 10.59 (s, 1H).

Example 33: 4',7-Dihydroxy-8-propylflavone (Compound 503)

Melting point: >300℃.

NMR (DMSO-d_6, δ): 0.92 (t, J=7.5Hz, 3H), 1.59 (m, 2H), 2.83 (t, J=7.5Hz, 2H), 6.68 (s, 1H), 6.89-6.94 (m, 3H), 7.69 (d, J=8.7Hz, 1H), 7.85 (d, J=8.7Hz, 2H), 10.20 (br, 1H), 10.45 (br, 1H).

Example 34: 8-Propyl-3',4',7-trihydroxy-flavone (Compound 504)

Melting point: 293-294℃.

NMR (DMSO-d_6, δ): 0.97 (t, J=7.2Hz, 3H), 1.63 (m, 2H), 2.87 (t, J=6.9Hz, 2H), 6.62 (s, 1H), 6.90 (d, J=8.1Hz, 1H), 6.96 (d, J=9.0Hz, 1H), 7.37-7.41 (m,

2H), 7.73 (d, J=9.0Hz, 1H), 9.87 (br, 2H), 10.56 (br, 1H).

Example 35: 7-Hydroxy-3'-methoxy-8-propylflavone (Compound 507)

Melting point: 232-234℃.

NMR (DMSO-d_6, δ): 0.97 (t, J=7.5Hz, 3H), 1.67 (m, 2H), 2.88 (t, J=7.5Hz, 2H), 3.87 (s, 3H), 6.95 (s, 1H), 7.00 (d, J=8.7Hz, 1H), 7.17 (dd, J=1.5Hz, 8.4Hz, 1H), 7.48-7.55 (m, 2H), 7.66 (d, J=7.8Hz, 1H), 7.77 (d, J=8.7Hz, 1H), 10.60 (br, 1H).

Example 36: 3',7-Dihydroxy-4'-methoxy-8-propylflavone (Compound 511)

Melting point: 271-272℃.

NMR (DMSO-d_6, δ): 0.97 (t, J=7.5Hz, 3H), 1.64 (m, 2H), 2.88 (t, J=7.5Hz, 2H), 6.70 (s, 1H), 6.96 (d, J=8.7Hz, 1H), 7.12 (d, J=8.4Hz, 1H), 7.44 (d, J=2.1Hz, 1H), 7.52 (dd, J=2.1Hz, 8.4Hz, 1H), 7.74 (d, J=8.7Hz, 1H), 9.50 (br, 1H), 10.47 (br, 1H).

Example 37: 3'-Bromo-4',7-dihydroxy-5'-methoxy-8-propylflavone (Compound 512)

Melting point: 250-255℃.

NMR (DMSO-d_6, δ): 0.77 (t, J=7.5Hz, 3H), 1.40 (m, 2H), 2.62 (t, J=6.9Hz, 2H), 3.72 (s, 3H), 6.72-6.76 (m, 2H), 7.35 (d, J=1.8Hz, 1H), 7.50 (d, J=9.0Hz, 1H), 7.56 (d, J=1.8Hz, 1H), 10.17 (br, 1H), 10.39 (brs, 1H).

Example 38: 7-Hydroxy-2'-isopropoxy-8-propylflavone (Compound 513)

Melting point: 199-200℃.

NMR (DMSO-d_6, δ): 0.93 (t, J=7.5Hz, 3H), 1.33 (d, J=6.0Hz, 6H), 1.60 (m, 2H), 2.82 (t, J=7.5Hz, 2H), 4.81 (m, 1H), 6.84 (s, 1H), 7.00 (d, J=8.7Hz, 1H),

7.14 (t, J=7.8Hz, 1H), 7.26 (d, J=8.1Hz, 1H), 7.53 (m, 1H), 7.75 (d, J=8.7Hz, 1H), 7.84 (dd, J=1.5Hz, 7.8Hz, 1H), 10.58 (br, 1H).

Example 39: 4',7-Dihydroxy-3'-methyl-8-propylflavone (Compound 521)

Melting point: 191-192℃.

NMR (DMSO-d_6, δ): 0.99 (t, J=7.5Hz, 3H), 1.64 (m, 2H), 2.21 (s, 3H), 2.87 (t, J=7.5Hz, 2H), 6.72 (s, 1H), 6.96 (d, J=8.7Hz, 2H), 7.73 (d, J=8.7Hz, 2H), 7.79 (s, 1H), 10.23 (s, 1H), 10.55 (s, 1H).

Example 40: 4',7-Dihydroxy-3',8-dipropylflavone (Compound 523)

Melting point: 228-230℃.

NMR (DMSO-d_6, δ): 0.94 (t, J=7.2Hz, 3H), 0.99 (t, J=7.2Hz, 3H), 1.63 (m, 4H), 2.59 (t, J=7.5Hz, 2H), 2.87 (t, J=8.4Hz, 2H), 6.73 (s, 1H), 6.94-7.99 (m, 2H), 7.71-7.77 (m, 3H), 10.12 (br, 1H), 10.54 (br, 1H).

Example 41: 2'-Fluoro-7-hydroxy-8-propylflavone (Compound 525)

Melting point: 204-207℃.

NMR (DMSO-d_6, δ): 0.94 (t, J=7.5Hz, 3H), 1.61 (m.2H), 2.82 (t, J=7.5Hz, 2H), .68 (s, 1H), 7.02 (d, J=8.7Hz, 1H), 7.43-7.50 (m, 2H), 7.5 (m, 1H), 7.78 (d, J=8.4Hz, 1H), 7.97 (m, 1H), 10.65 (br,1H).

Example 42: 4'-Fluoro-7-hydroxy-8-propylflavone (Compound 527)

Melting point: 243℃.

NMR (DMSO-d_6, δ): 0.95 (t, J=7.5Hz, 4H), 1.64 (m, 2H), 2.87 (t, J=6.9Hz, 2H), 6.99 (d, J=8.7Hz, 1H), 7.44 (t, J=8.7Hz, 2H), 7.75 (d, J=8.7Hz, 1H), 8.10 (dd, J=2.1Hz, 8.7Hz, 1H), 10.59 (s, 1H).

Example 43: 3'-Bromo-4',7-dihydroxy-8-propylflavone (Compound 536)

Melting point: 267-270℃.

NMR (DMSO-d_6, δ): 1.00 (t, J=7.5Hz, 3H), 1.64 (m, 2H), 2.89 (t, J=7.5Hz, 2H), 6.81 (s, 1H), 6.99 (d, J=8.7Hz, 1H), 7.18 (d, J=8.7Hz, 1H), 7.74 (d, J=8.7Hz, 1H), 7.91 (d, J=8.7Hz, 1H), 8.15 (s, 1H), 10.56 (s, 1H), 11.17 (s,1H).

Example 44: 7-Hydroxy-2'-nitro-8-propylflavone (Compound 545)

Melting point: 117-118℃.

NMR (DMSO-d_6, δ): 0.87 (t, J=7.5Hz, 3H), 1.43 (m, 2H), 2.51 (t, J=7.2Hz, 2H), 6.97 (s,1H), 7.01 (d, J=8.7Hz, 1H), 7.78-7.95 (m, 4H), 8.16 (dd, J=1.5Hz, 7.8Hz, 1H), 10.68 (s, 1H).

Example 45: 7-Hydroxy-3'-methoxy-2'-nitro-8-propylflavone (Compound 548)

Melting point: 236℃.

NMR (DMSO-d_6, δ): 0.93 (t, J=7.5Hz, 3H), 1.48 (m, 2H), 2.60 (t, J=6.9Hz, 2H), 3.98 (s, 3H), 6.66 (s, 1H), 7.01 (d, J=8.7Hz, 1H), 7.52 (d, J=7.5Hz, 1H), 7.61 (d, J=8.7Hz, 1H), 7.73-7.80 (m, 2H), 10.68 (br, 1H).

Example 46: 7-Hydroxy-4'-methoxy-3'-nitro-8-propylflavone (Compound 553)

Melting point: 273℃ (decomposition).

NMR (DMSO-d_6, δ): 1.00 (t, J=7.5Hz, 3H), 1.64 (m, 2H), 2.87 (t, J=7.2Hz, 2H), 4.04 (d,3H), 7.00 (s, 1H), 7.59 (d, J=8.7Hz, 1H), 7.76 (d, J=9.0Hz, 1H), 8.33 (dd, J=2.4Hz, 9.0Hz, 1H), 8.53 (s, J=2.4Hz, 1H), 10.62 (s,1H).

Example 47: 4',7-Dihydroxy-3'-nitro-8-propylflavone (Compound 554)

Melting point: 263-264℃.

NMR (DMSO-d_6, δ): 1.01 (t, J=7.8Hz, 3H), 1.64 (m, 2H), 2.87 (t, J=7.8Hz,

2H), 6.90 (s, 1H). 6.99 (s, J=8.7Hz, 1H), 7.29 (s, J=9.0Hz, 1H). 7.75 (d, J=8.7Hz, 1H), 8.20 (dd, J=1.8Hz, 9.0Hz, 1H), 8.53 (d, J=1.8Hz, 1H). 10.63 (s, 1H).

Example 48: 7-Hydroxy-3'-methoxy-4'-nitro-8-propylflavone (Compound 555)

Melting point: 244-245℃.

NMR (DMSO-d_6, δ): 0.97 (t, J=7.5Hz, 3H), 1.65 (m, 2H), 2.89 (t, J=7.5Hz, 2H), 4.07 (s, 3H), 7.02 (d, J=9.0Hz, 1H), 7.19 (s, 1H), 7.75-7.80 (m, 2H), 8.19 (d, J=8.7Hz, 1H), 10.67 (br, 1H).

Example 49: 7-Hydroxy-8-propylflavone (Compound 557)

Melting point: 224-226℃.

NMR (DMSO-d_6, δ): 0.97 (t, J=7.2Hz, 3H), 1.65 (m, 2H), 2.89 (t, J=6.9Hz, 2H), 6.93 (s, 1H), 7.00 (d, J=8.7Hz, 1H), 7.59-7.62 (m, 3H), 7.77 (s, J=8.7Hz, 1H), 8.04-8.07 (m, 2H), 10.65 (s, 1H).

Example 50: 7-Hydroxy-3'-phenoxy-8-propylflavone (Compound 558)

Melting point: 198-201℃.

NMR (DMSO-d_6, δ): 0.78 (t, J=7.5Hz, 3H), 1.50 (m, 2H), 2.71 (t, J=7.2Hz, 2H), 6.94 (s, 1H), 6.98 (d, J=8.7Hz, 1H), 7.14 (d, J=7.5Hz, 2H), 7.22-7.26 (m, 2H), 7.43-7.49 (m, 2H), 7.57-7.63 (m, 2H), 7.75 (d, J=8.4Hz, 1H), 7.83 (d, J=8.7Hz, 1H), 10.64 (br, 1H).

Example 51: 4',7-Dihydroxy-3'-propoxy-8-propylflavone (Compound 560)

Melting point: 220-222℃.

NMR (DMSO-d_6, δ): 0.95-1.03 (m, 6H), 1.62 (m, 2H), 1.78 (m, 2H), 2.85 (t, J=7.2Hz, 2H), 4.04 (t, J=6.6Hz, 2H), 6.79 (s, 1H), 6.95 (d, J=8.7Hz, 2H),

7.49-7.52 (m, 2H), 7.72 (d, J=8.7Hz, 1H), 9.75 (brs, 1H), 10.51 (s, 1H).

Example 52: 3'-Isopropoxy-4',7-dihydroxy-8-propylflavone (Compound 561)

Melting point: 260-261℃.

NMR (DMSO-d_6, δ): 1.25 (t, J=7.2Hz, 3H), 1.38 (d, J=6.6Hz, 6H), 1.64-1.73 (m, 4H), 4.69 (m, 1H), 6.69 (s, 1H), 6.94 (d, J=8.4Hz, 1H), 7.06 (d, J=8.4Hz, 1H), 7.40 (d, J=1.8Hz, 1H), 7.51 (dd, J=1.8Hz, 8.4Hz, 1H), 7.98 (d, J=8.4Hz, 1H).

Example 53: 3'-Butoxy-4',7-dihydroxy-8-propylflavone (Compound 563)

Melting point: 215-217℃.

NMR (DMSO-d_6, δ): 0.92-0.99 (m, 6H), 1.45 (m, 2H), 1.61 (m, 2H), 1.72 (m, 2H), 2.85 (t, J=8.0Hz, 2H), 4.07 (t, J=6.6Hz, 2H), 6.79 (s, 1H), 6.94 (d, J=8.5Hz, 2H), 7.48-7.52 (m, 2H), 7.72 (d, J=8.5Hz, 1H).

Example 54: 3'-Decanyloxy-4',7-dihydroxy-8-propylflavone (Compound 582)

形状: Syrup.

NMR (DMSO-d_6, δ): 0.85 (t, J=6.9Hz, 3H), 0.98 (t, J=7.2Hz, 3H), 1.24-1.35 (m, 14H), 1.64 (m, 2H), 75 (m, 2H), 2.86 (m, 2H), 4.08 (t, J=6.6Hz, 2H), 6.83 (s, 1H), 6.95-6.98 (m, 2H), 7.50-7.54 (m, 2H), 7.74 (d, J=8.7Hz, 1H), 9.81 (s, 1H), 10.57 (s, 1H).

Example 55: 8-Butyl-4',7-dihydroxyflavone (Compound 593)

Melting point: 233-236℃.

NMR (DMSO-d_6, δ): 0.93 (t, J=7.2Hz, 3H), 1.39 (m, 2H), 1.58 (m, 2H), 2.89 (t, J=7.2Hz, 2H), 6.72 (s, 1H), 6.93-6.98 (m, 2H), 7.73 (d, J=8.7Hz, 1H), 7.89 (d, J=9.0Hz, 1H).

Example 56: 4',7-Dihydroxy-3'-methoxy-8-methylflavone (Compound 680)

Melting point: 170℃.

NMR (DMSO-d_6, δ): 2.35 (s, 3H), 3.89 (s, 3H), 6.83 (s, 1H), 6.94-7.00 (m, 2H), 7.55-7.57 (m, 2H), 7.73 (d, J=8.4Hz, 1H), 10.57 (s, 1H).

Example 57: 4',7-Dihydroxy-8-ethyl-3'-methoxyflavone (Compound 681)

Melting point: 255-257℃.

NMR (DMSO-d_6, δ): 1.22 (t, J=7.5Hz, 3H), 5.81 (, J=7.5Hz, 2H), 6.85 (s, 1H), 6.95-6.99 (m, 2H), 7.52-7.55 (m, 2H), 7.73 (d, J=8.4Hz, 1H), 9.90 (s, 1H), 10.59 (s, 1H).

Example 58: 8-Butyl-4',7-dihydroxy-3'-methoxyflavone (Compound 684)

Melting point: 228-231℃.

NMR (DMSO-d_6, δ): 0.93 (t, J=7.2Hz, 3H), 1.39 (m, 2H), 1.60 (m, 2H), 2.89 (t, J=7.5Hz, 2H), 3.89 (s, 3H), 6.82 (s, 1H), 6.93-6.98 (m, 2H), 7.51-7.54 (m, 2H), 7.73 (s, J=8.4Hz, 1H), 9.85 (s, 1H), 10.51 (s, 1H).

Example 59: 4',7-Dihydroxy-8-isopentyl-3'-methoxyflavone (Compound 690)

Melting point: 225-227℃.

NMR (DMSO-d_6, δ): 0.96 (d, J=6.6Hz, 6H), 1.47 (m, 2H), 1.65 (m, 1H), 2.89 (t, J=7,5Hz, 2H), 3.89 (s, 3H), 6.82 (s, 1H), 6.92-6.98 (m, 2H), 7.51-7.54 (m, 2H), 7.73 (d, J=8.7Hz, 1H), 9.86 (s, 1H), 10.52 (s, 1H).

Example 60: 8-Benzyl-4',7-dihydroxy-3'-methoxyflavone (Compound 712)

Melting point: 281-282℃.

NMR (DMSO-d_6, δ): 3.78 (s, 3H), 4.26 (s, 2H), 6.83 (s, 1H), 6.90 (d, J=8.1Hz,

1H), 7.04 (d, J=8.7Hz. 1H), 7.14 (m, 1H), 7.20-7.26 (m, 4H), 7.41-7.46 (m, 2H), 7.81 (d, J=8.7Hz, 1H). 9.88 (br. 1H), 10.82 (br, 1H).

Example 61: 7-Hydroxy-8-methyl-2-(1-naphthyl)chromone (Compound 764)

Melting point: 250-253℃.

NMR (DMSO-d_6, δ): 1.87 (s, 3H), 6.52 (s, 1H), 7.00 (d, J=8.7Hz, 1H), 7,58-7.66 (m, 3H), 7.80 (d, J=8.7Hz, 1H), 7.85 (dd, J=1.2Hz, 7.5Hz, 1H), 8.03-8.15 (m, 3H), 10.68 (br. 1H).

Example 62: 7-Hydroxy-2-(2-hydroxy-1-naphthyl)-8-methylchromone (Compound 766)

NMR (DMSO-d_6, δ): 2.10 (s, 3H), 6.60 (d, J=8.7Hz, 1H), 7.11 (s, 1H), 7.60-7.69 (m, 3H), 7.73-7.81 (m, 2H), 8.09 (d, J=8.1Hz, 1H), 8.31 (d, J=9.3Hz, 1H), 9.97 (s, 1H), 9.99 (s,1H).

Example 63: 7-Hydroxy-2-(3-hydroxy-2-naphthyl)-8-methylchromone (Compound 767)

Melting point: >300℃.

NMR (DMSO-d_6, δ): 2.38 (s, 3H), 7.00 (d, J=8.7Hz, 1H), 7.07 (s, 1H), 7.33-7.39 (m, 2H), 7.51 (m. 1H), 7.75-7.79 (m, 2H), 7.98 (d, J=8.1Hz, 1H), 8.47 (s, 1H), 10.62 (s,

Example 64: 7-Hydroxy-8-propyl-2-(2-pyridyl)chromone 1/2sulfate (Compound 785)

Melting point: 213-217℃.

NMR (DMSO-d_6, δ): 0.98 (t, J=7.5Hz, 3H), 1.66 (m, 2H), 2.92 (t, J=7.5Hz, 2H), 7.02 (d, J=8.7Hz, 1H), 7.10 (s, 1H), 7.63 (m, 1H), 7.80 (d, J=8.7Hz, 1H),

8.09-8.14 (m, 2H), 8.78 (d, J=4.8Hz, 1H), 10.70 (s, 1H).

Example 65: 7-Hydroxy-8-propyl-2-(3-pyridyl)chromone methanesulfonate (Compound 786)

Melting point: 278-279℃.

NMR (DMSO-d_6, δ): 0.97 (t, J=7.5Hz, 3H), 1.64 (m, 2H), 2.89 (t, J=8.1Hz, 2H), 6.98-7.06 (m, 2H), 7.65 (m, 1H), 7.78 (d, J=9.0Hz, 1H), 8.42 (m, 1H), 8.77 (m, 1H), 9.23 (d, J=2.1Hz, 1H), 10.68 (br, 1H).

Example 66: 7-Hydroxy-2-(2-methoxy-5-pyridyl)-8-propylchromone 1/2sulfate (Compound 787)

Melting point: 173-176℃.

NMR (DMSO-d_6, δ): 0.96 (t, J=7.5Hz, 3H), 1.63 (m, 2H), 2.87 (t, J=7.2Hz, 2H), 3.96 (s, 3H), 6.72 (s, 1H), 6.91-7.06 (m, 2H), 7.76 (d, J=8.7Hz, 1H), 8.32 (dd, J=2.4Hz, 8.7Hz, 1H), 8.86 (d, J=2.4Hz, 1H), 10.63 (br, 1H).

Example 67: 7-Hydroxy-8-propyl-2-(4-pyridyl)chromone methanesulfonate (Compound 788)

Melting point: 230-233℃.

NMR (DMSO-d_6, δ): 0.98 (t, J=7.2Hz, 3H), 1.65 (m, 2H), 2.35 (t, J=7.2Hz, 2H), 2.91 (s, 3H), 7.05 (s, 1H), 7.30 (d, J=8.7Hz, 1H), 7.80 (d, J=8.7Hz, 1H), 8.24 (dd, J=1.2Hz, 6.3Hz, 2H), 8.97 (dd, J=1.2Hz, 6.6Hz, 2H), 10.81 (br, 1H).

Example 68: 2-(2,4-dimethyl-5-pyrimidyl)-7-hydroxy-8-propylchromone (Compound 794)

Melting point: 179-182℃.

NMR (DMSO-d_6, δ): 0.91 (t, J=7.5Hz, 3H), 1.54 (m, 2H), 2.65 (s, 3H), 2.68 (s,

3H), 2.74 (t, J=7.2Hz, 2H), 6.62 (s, 1H), 7.02 (d, J=8.7Hz, 1H), 7.81 (d, J=8.7Hz, 1H), 8.87 (s, 1H), 10.70 (s, 1H).

Example 69: 7-Hydroxy-8-propyl-2-(2-pyrazyl)chromone methanesulfonate (Compound 795)

Melting point: 275-278℃.

NMR (DMSO-d_6, δ): 0.98 (t, J=7.5Hz, 3H), 1.67 (m, 2H), 2.92 (t, J=7.2Hz, 2H), 7.04 (d, J=8.7Hz, 1H), 7.10 (s, 1H), 7.80 (d, J=8.4Hz, 1H), 8.86-8.89 (m, 2H), 9.29 (d, J=1.2Hz, 1H), 10.75 (br, 1H).

Example 70: 7-Hydroxy-8-propyl-2-(2-quinolyl)chromone 1/2sulfate (Compound 802)

Melting point: 242-245℃.

NMR (DMSO-d_6, δ): 1.02 (t, J=7.2Hz, 3H), 1.71 (m, 2H), 2.97 (m, 2H), 7.05 (d, J=8.7Hz, 1H), 7.32 (s, 1H), 7.74 (m, 1H), 7.83 (d, J=8.7Hz, 1H), 7.89 (m, 1H), 8.10-8.17 (m, 2H), 8.40 (d, J=9.0Hz, 1H), 8.70 (d, J=8.7Hz, 1H), 10.73 (br, 1H).

Example 71: 7-Hydroxy-8-propyl-2-(1-propyl-2-pyridone-5-yl)chromone (Compound 814)

Melting point: >300℃.

NMR (DMSO-d_6, δ): 0.91 (t, J=7.5Hz, 3H), 0.96 (t, J=7.2Hz, 3H), 1.60 (m, 2H), 1.72 (m, 2H), 2.86 (t, J=7.2Hz, 2H), 4.42 (t, J=7.2Hz, 2H), 6.57 (d, J=9.6Hz, 1H), 6.74 (s, 1H), 6.97 (d, J=8.7Hz, 1H), 7.73 (d, J=8.7Hz, 1H), 7.99 (dd, J=2.4Hz, 9.6Hz, 1H), 8.46 (d, J=2.4Hz, 1H).

Example 72: 2-(1-Dimethylaminopropyl-2-pyridone-5-yl)-7-hydroxy-8-

propylchromone (Compound 815)

Melting point: 290-293°C.

NMR (DMSO-d_6, δ): 0.98 (t, J=7.5Hz, 3H), 1.61 (m, 2H), 1.84 (m, 2H), 2.13 (s, 6H), 2.22 (t, J=6.6Hz, 2H), 2.86 (t, J=7.8Hz, 2H), 4.05 (t, J=6.9Hz, 2H), 6.56 (d, J=9.3Hz, 1H), 6.73 (s, 1H), 6.97 (d, J=8.4Hz, 1H), 7.73 (d, J=8.4Hz, 1H), 8.01 (dd, J=2.4Hz, 9.3Hz, 1H), 8.45 (d, J=2.4Hz, 1H), 10.61 (br, 1H).

Example 73: 3'-Methoxy8-propyl4',5,7-trihydroxyflavone (Compound 832)

NMR (DMSO-d_6, δ): 0.95 (t, J=7.2Hz, 3H), 1.58 (m, 2H), 2.75 (t, J=6.9Hz, 2H), 3.89 (s, 3H), 6.29 (s, 1H), 6.88-6.95 (m, 2H), 7.54-7.57 (m, 2H), 10.00 (br, 2H), 12.90 (s, 1H).

Test Example: Inhibitory activity of the medicament of the present invention against P-GS1 phosphorylation by bovine cerebral TPK1:

A mixture containing 100 mM MES-sodium hydroxide (pH 6.5), 1 mM magnesium acetate, 0.5 mM EGTA, 5 mM β-mercaptoethanol, 0.02% Tween 20, 10% glycerol, 12 μg/ml P-GS1, 41.7 μM [γ-^{32}P] ATP (68 kBq/ml), bovine cerebral TPK1 and a compound shown in Table (a final mixture contained 1.7% DMSO deriving from a solution of a test compound prepared in the presence of 10% DMSO) was used as a reaction system. The phosphorylation was started by adding ATP, and the reaction was conducted at 25°C for 2 hours, and then stopped by adding 21% perchloric acid on ice cooling. The reaction mixture was centrifuged at 12,000 rpm for 5 minutes and adsorbed on P81 paper (Whatmann), and then the paper was washed four times with 75 mM phosphoric acid, three times with water and once with acetone. The paper was dried, and the residual radioactivity was

measured using a liquid scintillation counter. The results are shown in the table below. The test compound markedly inhibited the P-GS1 phosphorylation by TPK1. The results strongly suggest that the medicaments of the present invention inhibit the TPK1 activity, thereby suppress the Aβ neurotoxicity and the PHF formation, and that the medicaments of the present invention are effective for preventive and/or therapeutic treatment of Alzheimer disease and the above-mentioned diseases.

Table 9

Example	(Compound No.)	Inhibitory rate at 10 μM(%)
1	(455)	98.4
2	(682)	89.7
4	(45)	79.4
6	(55)	88.1
7	(58)	82.9
12	(148)	89.9
13	(158)	85.7
14	(161)	88.5
15	(162)	84.8
16	(264)	97.4
17	(310)	93.3
18	(342)	81.1
19	(343)	98.2
20	(347)	73.1
21	(351)	85.3

23	(365)	75.4
25	(386)	84.7
27	(389)	79.3
28	(391)	72.4
29	(392)	87.1
30	(393)	77.1
31	(491)	88.9
32	(502)	76.4
33	(503)	95.6
34	(504)	86.8
37	(512)	77.7
39	(521)	89.0
40	(523)	91.0
47	(554)	87.1
51	(560)	95.8
52	(561)	94.0
55	(593)	84.6
56	(680)	90.4
57	(681)	85.8
58	(684)	96.2
59	(690)	93.5
64	(785)	81.2
65	(786)	74.8
67	(788)	74.9
68	(794)	71.5
72	(815)	78.2

Formulation Example

(1) Tablets

The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 2	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft capsules

The ingredients below were mixed by an ordinary method and filled in soft capsules.

Compound of Example 2	30 mg
Olive oil	300 mg
Lecithin	20 mg

(3) Parenteral preparations

The ingredients below were mixed by an ordinary method to prepare injections contained in a 1 ml ample.

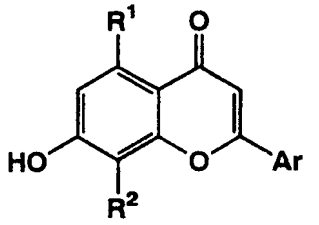
Compound of Example 1	0.1 mg
Sodium chloride	4 mg
Distilled water for infection	1 ml

Industrial Applicability

The medicaments of the present invention have TPK1 inhibitory activity and are useful for preventive and/or therapeutic treatment of diseases caused by TPK1 hyperactivity such as Alzheimer disease.

Claims

1. A medicament for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity or a neurodegenerative disease which comprises as an active ingredient a substance selected from the group consisting of a hydroxyflavone derivative represented by formula (I) and a salt thereof, and a solvate thereof and a hydrate thereof:



(I)

wherein R^1 represents hydrogen atom or hydroxyl group; R^2 represents hydrogen atom or a C_1-C_{18} alkyl group which may have one or more C_6-C_{14} aryl groups; and Ar represents a C_6-C_{14} aryl group which may be substituted or an aromatic heterocyclic group which may be substituted.

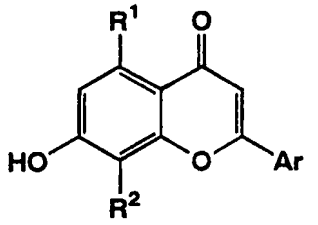
2. A medicament for preventive and/or therapeutic treatment of a neurodegenerative disease which comprises as an active ingredient a substance selected from the group consisting of a hydroxyflavone derivative represented by formula (I) according to claim 1 and a salt thereof, and a solvate thereof and a hydrate thereof.

3. The medicament according to claim 2, wherein the disease is selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic

encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration, and frontotemporal dementia.

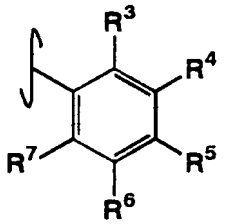
4. A tau protein kinase 1 inhibitor selected from the group of a hydroxyflavone derivative represented by formula (I) according to claim 1 and a salts thereof, and a solvate thereof and a hydrate thereof.

5. A hydroxyflavone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:



(I)

wherein R^1 represents hydrogen atom or hydroxyl group; R^2 represents hydrogen atom or a C_1-C_{18} alkyl group which may have one or more C_6-C_{14} aryl groups; and Ar represents a C_6-C_{14} aryl group which may be substituted or an aromatic heterocyclic group which may be substituted, and where R^2 is hydrogen atom, Ar represents a group represented by formula (II)



(II)

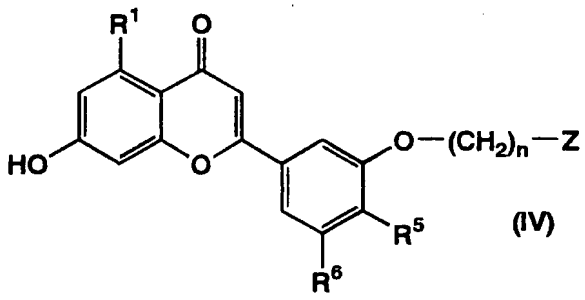
wherein R^3, R^4, R^5, R^6, and R^7, independently represent hydrogen atom, a C_1-C_{18} alkyl group which may be substituted, a C_1-C_{18} alkoxyl group which may be substituted, hydroxyl group, an acyloxy group which may be

substituted, carboxyl group, an alkoxycarbonyl group which may be substituted, a carbamoyl group which may be substituted, an alkylcarbonyl group which may be substituted, an amino group which may be substituted, nitro group, or a cyano group,

provided that any one of R^3, R^4, R^5, R^6, and R^7 represents a group represented by formula (III): $-X-(CH_2)_m-R^8$ wherein R^8 represents an amino group which may be substituted or a nitrogen-containing saturated heterocyclic group which may be substituted, X represents single bond or oxygen atom, and m is an integer of from 1 to 8; and

provided that those wherein R^1 is hydrogen atom, R^2 is methyl group, and Ar is phenyl group, a 3,4-methylenedioxyphenyl group, or a 3-pyridyl group, those wherein R^1 is hydrogen atom, R^2 is propyl group, and Ar is phenyl group having a carboxyl group or an ester group in the 4-position, and those wherein R^1 is hydroxyl group, R^2 is methyl group, and Ar is phenyl group, 4-hydroxyphenyl group, 4-methoxyphenyl group, or 3,4-dimethoxyphenyl group are excluded.

6. A hydroxyflavone derivative represented by formula (IV) or a salt thereof, or a solvate thereof or a hydrate thereof:



(IV)

wherein R^1 represents hydrogen atom or hydroxyl group; Z represents an amino group which may be substituted or a nitrogen-containing saturated

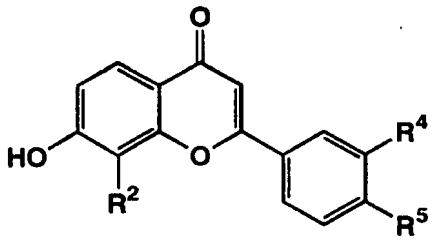
heterocyclic group which may be substituted; n represents an integer of from 1 to 8; R^5 represents hydrogen atom, a C_1-C_{15} alkoxyl group; and R^6 represents hydrogen atom or hydroxyl group.

7. The hydroxyflavone derivative according to claim 6 or a salt thereof, or a solvate thereof or a hydrate thereof, wherein n is 2 or 3.

8. The hydroxyflavone derivative according to claim 6 or a salt thereof, or a solvate thereof or a hydrate thereof, wherein R^5 is hydrogen atom or methoxy group.

9. The hydroxyflavone derivative according to claim 6 or a salt thereof, or a solvate thereof or a hydrate thereof, wherein Z is dimethylamino group, piperazinyl group which may be substituted, or piperidinyl group which may be substituted.

10. A hydroxyflavone derivative represented by formula (V) or a salt thereof, or a solvate thereof or a hydrate thereof:



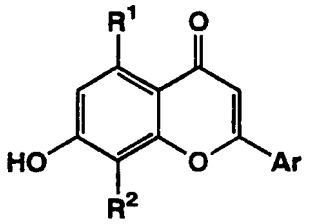
(V)

wherein R^2 represents hydrogen atom or a C_1-C_{18} alkyl group which may have one or more C_6-C_{14} aryl groups; R^4 represents a C_1-C_{18} alkyl group which may be substituted, a C_1-C_{18} alkoxyl group which may be substituted, hydroxyl group, an acyloxy group which may be substituted, carboxyl group, an alkoxycarbonyl group which may be substituted, a carbamoyl group which may be substituted, an alkylcarbonyl group which may be substituted, an amino group which may be substituted, nitro group, or a cyano group; and R^5

represents hydrogen atom, hydroxyl group, methoxy group, or nitro group.

11. The hydroxyflavone derivative according to claim 10 or a salt thereof, or a solvate thereof or a hydrate thereof, wherein R^4 is a C_1-C_{18} alkyl group which may be substituted, a C_1-C_{18} alkoxyl group which may be substituted, hydroxyl group, nitro group, or a cyano group.

12. A hydroxyflavone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:



(I)

wherein R^1 represents hydrogen atom or hydroxyl group; R^2 represents hydrogen atom or a C_1-C_{18} alkyl group which may have one or more C_6-C_{14} aryl groups; and Ar represents an aromatic heterocyclic group which may be substituted, provided that those wherein R^1 is hydrogen atom; R^2 is methyl group, and Ar is a pyridyl group are excluded.

13. A hydroxyflavone derivative or a salt thereof, or a solvate thereof or a hydrate thereof which is selected from the group consisting of:

7-hydroxy-3'-(3-(1-piperidyl)propyloxy)-8-propylflavone,

4',7-dihydroxy-3'-methoxy-8-propylflavone,

7-hydroxy-8-methyl-3'-(3-(1-piperidyl)propyloxy)flavone,

7-hydroxy-4'-nitro-3'-(3-(1-piperidyl)propyloxy)-8-propylflavone,

4',7-dihydroxy-3'-methoxy-8-methylflavone, and

7-hydroxy-8-propyl-2-(4-pyridyl)chromone.

14. A medicament comprising a substance selected from the group

consisting of a hydroxyflavone derivative according to any one of claims 5 to 13 and a salt thereof, and a solvate thereof and a hydrate thereof.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/JP 99/05223

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D311/30 A61K31/35 C07D407/04 C07D409/04 C07D405/04
C07D413/04 C07D417/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BAURES, PAUL W. ET AL: "Discovering transthyretin amyloid fibril inhibitors by limited screening" BIOORG. MED. CHEM. (1998), 6(8), 1389-1401 ,August 1998 (1998-08), XP002129747 page 1393; table 3 ---	1-5,10, 11,13,14
X	JI ET AL.: "Interactions of flavonoids..." J.MED.CHEM, vol. 39, 1996, pages 781-788, XP002129748 table 1 ---	1-5,10, 11,14
X	CUSHMAN ET AL.: "Sythesis and protein-tyrosine kinase..." J.MED.CHEM., vol. 34, 1991, pages 798-806, XP002129749 table II ---	1-5,14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 2000	10.03.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

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INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/JP 99/05223

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	RASTELLI G ET AL: "Theoretical and experimental study of flavones as inhibitors of xanthine oxidase" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY.CHIMICA THERAPEUTICA,FR,EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, vol. 30, no. 2, 1 January 1995 (1995-01-01), pages 141-146, XP004040129 ISSN: 0223-5234 table 1 ---	1-5,10, 11,14
X	NAMGOONG S Y ET AL: "EFFECTS OF NATURALLY OCCURRING FLAVONOIDS ON MITOGEN-INDUCED LYMPHOCYTE PROLIFERATION AND MIXED LYMPHOCYTE CULTURE" LIFE SCIENCES,US,ELMSFORD, NY, vol. 54, no. 5, 1 January 1994 (1994-01-01), pages 313-320, XP002065684 ISSN: 0024-3205 table 1 ---	1-5,10, 11,14
X	DATABASE WPI Section Ch, Week 199806 Derwent Publications Ltd., London, GB; Class B02, AN 1998-059127 XP002129753 & JP 09 301915 A (SANKYO CO LTD), 25 November 1997 (1997-11-25) abstract ---	1-5,10, 11,14
X	EP 0 832 886 A (ADIR) 1 April 1998 (1998-04-01) see page 5, formula V ---	1-5,10, 11
X	DE 21 42 527 A (FISONS LTD.) 2 March 1972 (1972-03-02) claim 1 ---	1-5,12, 14
X	EP 0 758 649 A (KUREHA CHEMICAL IND CO LTD) 19 February 1997 (1997-02-19) claim 1 ---	1-5,12, 14
X	CHEMICAL ABSTRACTS, vol. 106, no. 17, 27 April 1987 (1987-04-27) Columbus, Ohio, US; abstract no. 138214, LE FLOCH: "Synthesis of dihydroxy..." XP002129750 & Tet.Lett., 1986, 27(4), 2751-2752 abstract ---	1-5,12
	-/--	

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INTERNATIONAL SEARCH REPORT

Inter ɔnal Application No
PCT/JP 99/05223

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 54, no. 14, 25 July 1960 (1960-07-25) Columbus, Ohio, US; PACHECO ET AL.: "Condensation reactions with ethyl nicotinoylacetate" column 14245; XP002129751 & Bull.soc.chim.Fr. 1960, 95-98 abstract	1-5,12
X	CHEMICAL ABSTRACTS, vol. 128, no. 6, 9 February 1998 (1998-02-09) Columbus, Ohio, US; abstract no. 61457, PATONAY ET AL.: "Synthesis of novel ..." XP002129752 & Bull.soc.chim.Fr.(1997),134(7), 653-667 abstract	1-5,12
A	EP 0 616 032 A (MITSUBISHI CHEM IND) 21 September 1994 (1994-09-21) the whole document	1-14

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 99/05223

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-5,14 (all part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5,14 (all part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to:
Use of compounds as defined under formula I in claims 1-5, 14 for (manufacturing a medicament) for treatment of Alzheimers disease and the like as well as compounds defined in claims 6-13.

In this context it is further noted that the definition in claim 5 (in particular with respect to the proviso's) appear inconsistent to the extent that a complete search is impossible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/JP 99/05223

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